

S1B16

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
4 July 2002 (04.07.2002)

PCT

(10) International Publication Number
WO 02/051841 A1(51) International Patent Classification⁷: C07D 453/02,
A61K 31/439, A61P 43/00, C07D 471/08 // (C07D
471/08, 221:00, 209:00)Maria Antonia [ES/ES]; Paris, 50, 1^o-4^o, E-08029
Barcelona (ES). FERNANDEZ FORNER, Maria Dolors
[ES/ES]; Roger de Flor, 221, 5^o 4^o, E-08025 Barcelona
(ES). PRAT QUINONES, Maria [ES/ES]; Calle Andrea
Doria, 2, 1^o 1^o, E-08003 Barcelona (ES).

(21) International Application Number: PCT/EP01/15169

(74) Agents: SRINIVASAN, Ravi, Chandran et al.; J.A.
Kemp & Co., 14 South Square, Gray's Inn, London WC1R
5JJ (GB).(22) International Filing Date:
20 December 2001 (20.12.2001)

(25) Filing Language:

English

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, CZ, CA, CI, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZM, ZW.

(26) Publication Language:

English

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent(30) Priority Data:
200003084 22 December 2000 (22.12.2000) ES

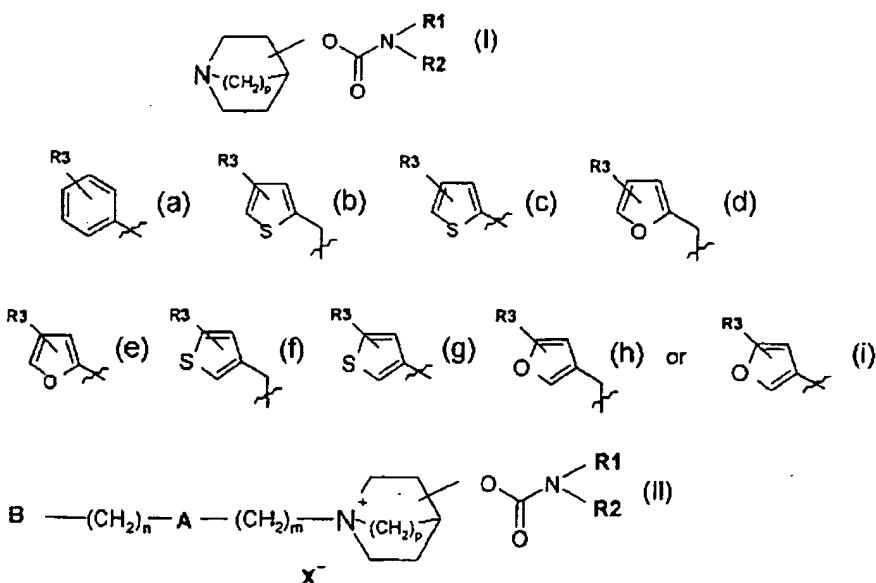
[Continued on next page]

(71) Applicant (for all designated States except US): ALMIRALL PRODESFARMA, S.A. [ES/ES]; Ronda del General Mitre 151, E-08022 Barcelona (ES).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BUIL ALBERO,

(54) Title: QUINUCLIDINE CARBAMATE DERIVATIVES AND THEIR USE AS M3 ANTAGONISTS



(57) Abstract: A compound which is a carbamate of formula (I), wherein R1 represents (a), (b), (c), (d), (e), (f), (g), (h) or (i); R2 represents a benzyl, phenethyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl or thiophen-3-ylmethyl group or a straight or branched alkyl group having 3 or 8 carbon atoms, an alkenyl group having 3 to 8 carbon atoms, or a cycloalkyl group of 3 to 6 carbon atoms; p is 1 or 2 and the substitution in the azoniabicyclic ring may be in the 2, 3 or 4 position including all possible configurations of the asymmetric carbons; or a pharmaceutically acceptable salt thereof. The pharmaceutically acceptable salt may be of formula (II).

WO 02/051841 A1



(BH, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, MI., MR,
NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

- with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

QUINUCLIDINE CARBAMATE DERIVATIVES AND THEIR USE AS M₃ ANTAGONISTS

5 This invention relates to new therapeutically useful quinuclidine carbamate derivatives, to some processes for their preparation and to pharmaceutical compositions containing them.

10 The novel structures according to the invention are antimuscarinic agents with a potent and long lasting effect. In particular, these compounds show high affinity for muscarinic M₃ receptors. This subtype of muscarinic receptor is present in glands and smooth muscle and mediates the excitatory effects of the parasympathetic system on glandular secretion and on the contraction of visceral smooth muscle (Chapter 6, *Cholinergic Transmission*, in H.P. Rang et al., *Pharmacology*, Churchill Livingstone, New York, 1995).

15 M₃ antagonists are therefore known to be useful for treating diseases characterised by an increased parasympathetic tone, by excessive glandular secretion or by smooth muscle contraction (R.M. Eglen and S.S. Hegde, (1997), *Drug News Perspect.*, 10(8):462-469).

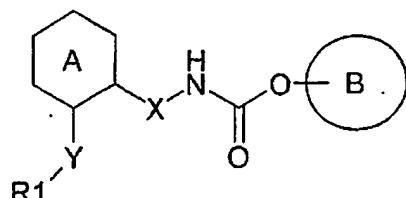
20 Examples of this kind of diseases are respiratory disorders such as chronic obstructive pulmonary disease (COPD), bronchitis, bronchial hyperreactivity, asthma, cough and rhinitis; urological disorders such as urinary incontinence, pollakiuria, neurogenic or unstable bladder, cystospasm and chronic cystitis; gastrointestinal disorders such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulceration; and cardiovascular disorders such as vagally induced sinus bradycardia 25 (Chapter 7, *Muscarinic Receptor Agonists and Antagonists*, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 10th edition, McGraw Hill, New York, 2001).

30 The compounds of the invention can be used alone or in association with other drugs commonly regarded as effective in the treatment of these diseases. For example, they can be administered in combination with β₂-agonists, steroids, antiallergic drugs, phosphodiesterase IV inhibitors and/or leukotriene D₄ (LTD₄) antagonists for simultaneous, separate or sequential use in the treatment of a respiratory disease. The claimed compounds are useful for the treatment of the respiratory diseases detailed above in association with β₂-agonists, steroids, antiallergic drugs or 35 phosphodiesterase IV inhibitors.

Compounds with related structures have been described as anti-spasmodics and anti-cholinergic agents in several patents.

For example, in the patent application EP 747.355 carbamate derivatives are described which are represented by the following general formula

5



Wherein each symbol has the following meaning:

A ring is a benzene or a pyridine ring,

B ring is a nitrogen-containing saturated hetero-ring which may have a substituent on the nitrogen atom and which may have a cross-linking,

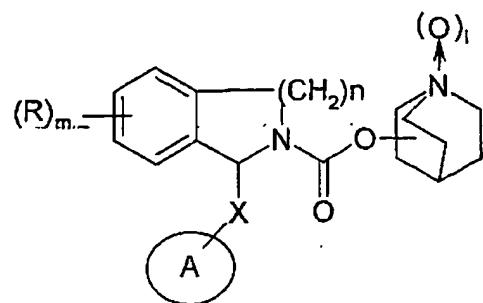
10 R1 is a phenyl group which may have a substituent, a cycloalkyl or cycloalkenyl group having 3 to 8 carbon atoms or a five- or six-membered nitrogen-containing heterocyclic group,

X is a single bond or a methylene group,

15 Y is a single bond, a carbonyl group, a methylene group which may be substituted with a hydroxyl group or a group represented by the formula $-S(O)_I-$, and I is an integer from 0-2.

These compounds clearly differ from the compounds of the present invention in terms of their structural characteristics, as they always have one hydrogen on the
20 nitrogen of the carbamate bond.

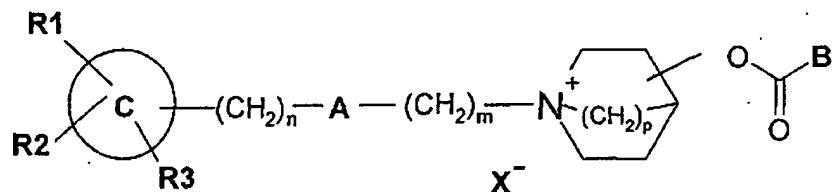
In addition, another patent application EP 801.067 discloses compounds represented by the formula



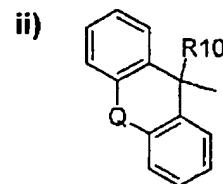
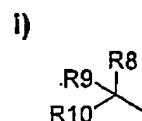
- Wherein **A** is an aryl group, a cycloalkyl group, a cycloalkenyl group or a heteroaryl group,
- X** is a single bond or a methylene group,
- 5 **I** is 0 or 1,
- n** is an integer of 1 or 2.

These compounds are also different from the compounds claimed in the present invention because the nitrogen of the carbamate group is included in a cyclic structure.

In WO 01/04118 are described compounds having the following general
10 formula



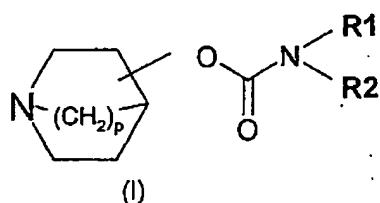
15 wherein **B** is a group of formula (I) or (ii):



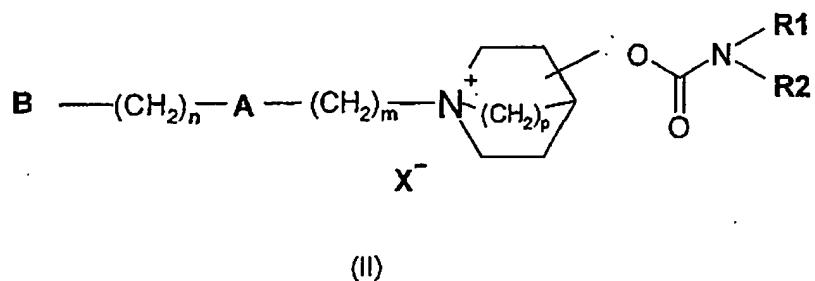
20 **C**, **A**, **R1**, **R2**, **R3**, **m**, **n**, **p**, **X**, **Q**, **R8**, **R9** and **R10** are defined in claim 1 of the cited application.

The present invention provides new compounds which are quinuclidine carbamate derivatives with potent antagonist activity at muscarinic M3 receptors and which have the chemical structure described in formula (I) or are pharmaceutically acceptable salts thereof including salts of formula (II).

25 Formula (I) represents a carbamate of the following general structure:

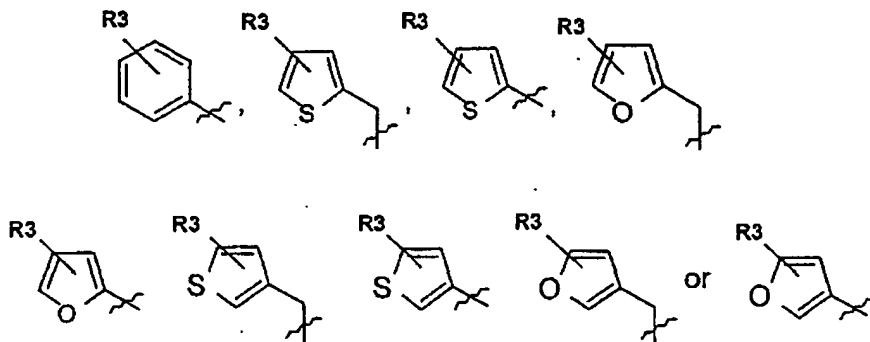


which may be quaternised to give a pharmaceutically acceptable salt of the carbamate of formula (I), in particular a salt of general formula (II)



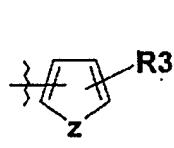
wherein;

10 R1 represents

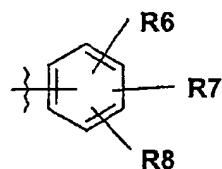


wherein R3 represents a hydrogen or halogen atom, or a straight or branched lower alkyl group or a cyano group;
15 R2 represents a benzyl-, phenethyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl, or thiophen-3-ylmethyl group, or a straight or branched alkyl group having 3 to 8 carbon atoms, an alkenyl group having 3 to 8 carbon atoms, or a cycloalkyl group of 3 to 6 carbon atoms;

- p is 1 or 2 and the substitution in the azoniabicyclic ring may be in the 2, 3 or 4 position including all possible configurations of the asymmetric carbons;
- m is an integer from 0 to 8;
- A represents a -CH₂-, -CH=CR4-, -CR4=CH-, -CO-, -O-, -S-, -S(O)-, SO₂, -NR4-, or
- 5 -CR4R5- group, wherein R4 and R5 each independently represent a hydrogen atom, a straight or branched lower alkyl group, or R4 and R5 together form an alicyclic ring;
- n is an integer from 0 to 4;
- B represents a hydrogen atom, an alkoxy group, a cycloalkyl group, -COOR4 or -OOCR4, wherein R4 is as defined above, or a cyano group, a naphthalenyl group, a
- 10 5,6,7,8-tetrahydronaphthalenyl group, a biphenyl group or a group of formula (i) or (ii)



(i)



(ii)

- 15 wherein Z represents O, N or S;
- R3 is as defined above; and
- R6, R7 and R8 each independently represent a hydrogen or halogen atom, or a hydroxy group, a phenyl group, -OR4, -SR4, -NR4R5, -NHCOR4, -CONR4R5, -CN, -NO₂, -COOR4 or -CF₃, or a straight or branched, substituted or unsubstituted lower
- 20 alkyl group, wherein R4 and R5 each independently represent a hydrogen atom, a straight or branched lower alkyl group, or R4 and R5 together form an alicyclic ring; or R6 and R7 together form an aromatic, alicyclic or heterocyclic ring; and
- X⁻ represents a pharmaceutically acceptable anion of a mono or polyvalent acid.

In the quaternary ammonium compounds of the present invention, including those represented by formula (II), an equivalent of an anion (X⁻) is associated with the positive charge of the N atom. X⁻ may be an anion of various mineral acids such as, for example, chloride, bromide, iodide, sulfate, nitrate, phosphate, or an anion of an organic acid such as, for example, acetate, trifluoroacetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulfonate and p-toluenesulfonate. X⁻ is preferably an anion selected from chloride, bromide, iodide, sulphate, nitrate, acetate, maleate, oxalate or succinate. More preferably X⁻ is chloride, bromide, trifluoroacetate or methanesulfonate.

The lower alkyl groups and moieties mentioned herein, unless otherwise specified, are straight or branched alkyl groups containing from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms. Preferred lower alkyl groups and moieties include methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl and t-butyl. Alkyl groups having 3 to 8 carbons mentioned herein, such as those present in the group R2, include n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, pentyl, hexyl, heptyl and octyl.

Optionally substituted lower alkyl groups mentioned herein include straight or branched alkyl groups containing from 1 to 6, preferably from 1 to 4, carbon atoms as mentioned above, which may be unsubstituted or substituted in any position by one or 10 more substituents, for example by 1, 2 or 3 substituents. When two or more substituents are present, each substituent may be the same or different. The substituent(s) are typically hydroxy or alkoxy groups.

Alkenyl groups having 3 to 8 carbon atoms mentioned herein, such as those present in the group R2, are straight or branched groups such as straight or branched 15 propenyl, butenyl, pentenyl, hexenyl, heptenyl or octenyl. The double bond may be in any position in the alkenyl group, such as on the terminal bond in relation to the carbamate group.

Alkoxy groups mentioned herein, such as those present in the group B, are typically lower alkoxy groups, that is groups containing from 1 to 6 carbon atoms, 20 preferably from 1 to 4 carbon atoms, the hydrocarbon chain being branched or straight. Preferred alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, sec-butoxy and t-butoxy.

Cycloalkyl groups and alicyclic groups mentioned herein, unless otherwise specified, typically contain from 3 to 8 carbon atoms, preferably from 3 to 6 carbon 25 atoms. Cycloalkyl groups and alicyclic rings of 3 to 6 carbon atoms include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The aromatic ring mentioned in relation to R6 and R7 typically contains from 5 to 14, preferably 5 to 10 carbon atoms. Examples of aromatic groups include cyclopentadienyl, phenyl and naphthalenyl.

30 The heterocyclic ring mentioned in relation to R6 and R7 is typically a 3 to 10 membered ring, such as a 5 or 6 membered ring, containing one or more heteroatoms selected from N, S and O. Typically, 1, 2, 3 or 4 heteroatoms are present, preferably 1 or 2 heteroatoms. Examples of heterocyclic rings include piperidyl, pyrrolidyl, azetidinyl, aziridyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, imidazolyl, 35 imidazolidinyl, pyrazolinyl, indolinyl, isoindolinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl,

quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, quinuclidinyl, triazolyl, pyrazolyl, triazolyl, tetrazolyl and thieryl.

As used herein a halogen atom includes a fluorine, chlorine, bromine or iodine atom, typically a fluorine, chlorine or bromine atom.

5 The compounds of the present invention represented by formula (I) and salts thereof such as those represented by formula (II), which may have one or more asymmetric carbons, include all the possible stereoisomers. The single isomers and mixtures of the isomers fall within the scope of the present invention.

Preferred carbamates of formula (I) are those wherein R1 is a phenyl, 10 thiophen-2-ylmethyl, thieryl or furan-2-ylmethyl group which is unsubstituted (i.e. R3 is hydrogen). If however R1 is substituted with a group R3 which is other than hydrogen, the substituent may be in the 2, 3, 4, 5 or, if R1 is a phenyl group, the 6 position. When R1 is phenyl, the substituent is preferably in the 4 position of the ring. The substituent R3 is preferably hydrogen, halogen or lower alkyl, preferably hydrogen, fluorine, 15 chlorine, methyl or ethyl and particularly preferably hydrogen, fluorine or methyl. Examples of substituted R1 groups include halo-phenyl, halo-thiophen-2-ylmethyl, halo-thieryl, halo-furan-2-ylmethyl, (C₁₋₄ alkyl)-phenyl, (C₁₋₄ alkyl)-thiophen-2-ylmethyl, (C₁₋₄ alkyl)-thieryl or (C₁₋₄ alkyl)-furan-2-ylmethyl. Specific examples include 4-fluorophenyl, 4-methylphenyl, 4-chlorophenyl, 4-ethylphenyl, 3-methylphenyl, 3-20 fluorophenyl, 3-chlorophenyl, 3-ethylphenyl, fluorothiophen-2-ylmethyl, fluorothieryl and fluorofuran-2-ylmethyl. Particularly preferred groups R1 include phenyl, 4-fluorophenyl, 4-methylphenyl, thiophen-2-ylmethyl, thieryl and furan-2-ylmethyl.

Preferred groups R2 include benzyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, furan-2-ylmethyl, phenethyl, pent-4-enyl, pentyl, butyl, allyl or cyclopentyl.

25 Preferred groups -NR1R2 in formula (I) include the groups -N(benzyl)(phenyl); -N(benzyl)(4-fluorophenyl); -N(benzyl)(p-tolylphenyl); -N(butyl)(phenyl); -N(phenyl)(thiophen-2-ylmethyl); -N(phenethyl)(phenyl); -N(pentyl)(phenyl); -N(pent-4-enyl)(phenyl); -N(phenyl)(thiophen-3-ylmethyl); -N(butyl)(thiophen-2-ylmethyl); -Nbisthiophen-2-ylmethyl; -N(furan-2-ylmethyl)(thiophen-2-ylmethyl); -N(allyl)(thiophen-30 2-ylmethyl); -N(cyclopentyl)(thiophen-2-ylmethyl); -N(furan-2-ylmethyl)(phenyl) and -Nbifuran-2-ylmethyl.

p-Is preferably 2. The substitution in the azoniabicyclo[2.2.2]octane is preferably in the 3 position. The substituted carbon atom may have (R) or (S) configuration, preferably (R) configuration.

35

The following compounds of general formula (I) are intended to illustrate but not to limit the scope of the present invention.

- Benzylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Benzyl(4-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Benzyl-p-tolylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Butylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
5 Phenylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Phenethylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Pentylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Pent-4-enylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Phenylthiophen-3-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
10 Butylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Bis-thiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Furan-2-ylmethyl-2-thiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Allylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
15 Cyclopentylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Furan-2-ylmethylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Bis-furan-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Benzylphenylcarbamic acid 1-azabicyclo[2.2.1]hept-4-yl ester
Benzylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-4-yl ester
20 and pharmaceutically acceptable salts thereof.

Preferred salts of formula (II) are those having the preferred definitions of R1, R2, -NR1R2 and p as for formula (I) above and the same location and configuration of the substituent on the azoniabicyclic ring.

25 Further, it is preferred that B represents a hydrogen atom or a substituted or unsubstituted phenyl, pyrrolyl, thienyl or furyl group, or a biphenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl or benzo[1,3]dioxolyl group, in particular a substituted or unsubstituted phenyl or thienyl group, such as a 2-thienyl group or a 3-thienyl group, particularly a 2-thienyl group.

30 The thienyl, pyrrolyl or furyl group may be unsubstituted or substituted with a group R3 as defined above. The substituent may be in the 2, 3, 4 or 5 position on the ring.

The phenyl group may be unsubstituted or substituted with one, two or three groups (R6 to R8) which may be in any position on the ring. Typically it is 35 unsubstituted or substituted with one group, for example in the 2, 3 or 4 position. Preferably, the substituents R6, R7 and R8 each independently represent a hydrogen or halogen atom, or a hydroxyl, methyl, tert-butyl, -CH₂OH, 3-hydroxypropyl, -OMe, -

- NMe₂, -NHCOMe, -CONH₂, -CN, -NO₂, -COOMe, or -CF₃ group, or R6 and R7 together form a 5- or 6-membered ring such as a phenyl or thiazolyl ring. More preferably, R6, R7 and R8 represent a hydrogen or halogen atom, or a hydroxyl, methyl, -CH₂OH, -OMe, -NMe₂, -NHCOMe, -CONH₂, -CN, -NO₂, -COOMe, or -CF₃ group, especially a hydrogen atom, a hydroxy group or a halogen atom, wherein the halogen atom is preferably fluorine. Examples of substituted phenyl groups which may represent B are tolyl including o-, m- and p-tolyl, 3-cyanophenyl, 2-, 3- and 4-hydroxyphenyl, 2-, 3- and 4-fluorophenyl and benzothiazolyl. B is particularly preferably a phenyl, 4-fluorophenyl or 3-hydroxyphenyl group.
- 10 Typically, n= 0 or 1; m is an integer from 1 to 6, particularly 1, 2 or 3; and A represents a -CH₂-, -CH=CH-, -CO-, -NMe-, -O- or -S- group, in particular a -CH₂-, -CH=CH-, or -O- group. Examples of suitable groups -(CH₂)_m-A-(CH₂)_n- include methylene, ethylene, allylene, n-propylene, i-propylene, butylene, 4-methyl pent-3-enylene, heptylene, ethyleneoxy, propyleneoxy, butyleneoxy, sulfanoylpropylene, 15 methylaminopropylene and 4-oxobutylene, preferably methylene, ethylene, allylene, n-propylene, heptylene, ethyleneoxy or propyleneoxy.

More preferred salts of formula (II) are those wherein the azoniabicyclo group is substituted on the nitrogen atom with a 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 4-phenylbutyl, 3-phenylpropyl, 3-[2-hydroxyphenoxy]propyl, 3-[4-fluorophenoxy]propyl, 2-benzyloxyethyl, 3-pyrrol-1-ylpropyl, 2-thien-2-ylethyl, 3-thien-2-ylpropyl, 3-phenylaminopropyl, 3-(methylphenylamino)propyl, 3-phenylsulfanylpropyl, 3-o-tolyloxypropyl, 3-(2,4,6-trimethylphenoxy)propyl, 3-(2-tert-butyl-6-methylphenoxy)propyl, 3-(biphenyl-4-yloxy)propyl, 3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)-propyl, 3-(naphthalen-2-yloxy)propyl, 25 3-(naphthalen-1-yloxy)propyl, 3-(2-chlorophenoxy)propyl, 3-(2,4-difluorophenoxy)propyl, 3-(3-trifluoromethylphenoxy)propyl, 3-(3-cyanophenoxy)propyl, 3-(4-cyanophenoxy)propyl, 3-(3-methoxyphenoxy)propyl, 3-(4-methoxyphenoxy)propyl, 3-(benzo[1,3]dioxol-5-yloxy)propyl, 3-(2-carbamoylphenoxy)propyl, 3-(3-dimethylaminophenoxy)propyl, 30 3-(4-nitrophenoxy)propyl, 3-(3-nitrophenoxy)propyl, 3-(4-acetylaminophenoxy)propyl, 3-(3-methoxycarbonylphenoxy)propyl, 3-[4-(3-hydroxypropyl)phenoxy]propyl, 3-(2-hydroxymethylphenoxy)propyl, 3-(3-hydroxymethylphenoxy)propyl, 3-(4-hydroxymethylphenoxy)propyl, 3-(2-hydroxyphenoxy)propyl, 3-(4-hydroxyphenoxy)propyl, 3-(3-hydroxyphenoxy)propyl, 4-oxo-4-thien-2-ylbutyl, 35 3-(1-methyl-[1H]-imidazol-2-ylsulfanyl)propyl, 3-(benzothiazol-2-yloxy)propyl, 3-benzyloxypropyl, 6-(4-phenylbutoxy)hexyl, 4-phenoxybutyl or 2-benzyloxyethyl group. Especially preferred salts are those wherein the azoniabicyclo group is substituted on

the nitrogen atom with a 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 3-thiophen-2-ylpropyl, 1-allyl or 1-heptyl group.

The following salts of general formula (II) are intended to illustrate but not to limit the scope of the present invention.

- 5 3-(R)(Benzylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane; bromide
10 1-Allyl-3-(R)(benzylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide
15 3-(R)(Benzylphenylcarbamoyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide
20 3-(R)(Benzylphenylcarbamoyloxy)-1-(3-thiophen-2-yl-propyl)-1-azoniabicyclo[2.2.2]octane; bromide
25 3-(R)(Benzylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide
30 3-(R)(Butylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane; bromide
35 1-Allyl-3-(R)(butylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide
40 3-(R)(Butylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide
45 3-(R)(Butylphenylcarbamoyloxy)-1-(3-hydroxyphenoxy)-1-azoniabicyclo[2.2.2]octane; bromide
50 3-(R)(Butylphenylcarbamoyloxy)-1-[3-(4-fluorophenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; bromide
55 3-(R)(Butylphenylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide
60 3-(R)(Butylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide
65 3-(R)(Phenylthiophen-2-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azonia
70 bicyclo[2.2.2]octane; bromide
75 1-(2-Phenoxy-ethyl)-3-(R)-(phenyl-thiophen-2-ylmethyl-carbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide
80 1-Allyl-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane, bromide
85 3-(R)(Phenethylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

- 1-Heptyl-3-(R)(pent-4-enylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane;
trifluoroacetate

1-Allyl-3-(R)-(phenyl-thiophen-3-ylmethyl-carbamoyloxy)-1-azonia-bicyclo[2.2.2]octane;
trifluoroacetate

5 3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azonia
bicyclo[2.2.2]octane; bromide

1-(2-Phenoxyethyl)-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo
[2.2.2]octane; bromide

10 3-(R)(Bis-thiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo
[2.2.2]octane; bromide

3-(R)(Bis-thiophen-2-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo
[2.2.2]octane; bromide

15 1-Allyl-3-(R)(allylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane;
trifluoroacetate

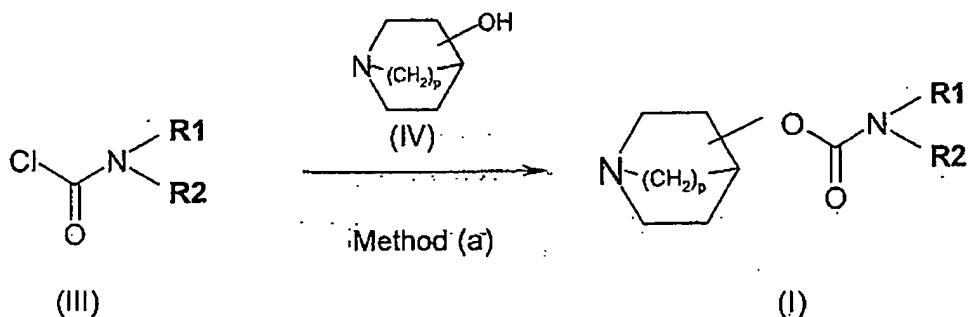
3-(R)(Cyclopentylthiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azonia
bicyclo[2.2.2]octane; trifluoroacetate

3-(R)(Furan-2-ylmethylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo
[2.2.2]octane; trifluoroacetate

20 1-Allyl-3-(R)(bis-furan-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane;
trifluoroacetate

The present invention also provides processes for preparing compounds of formulas (I) and (II).

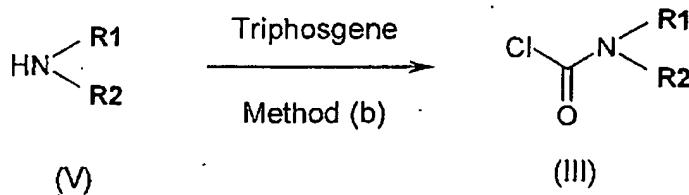
Compounds of general formula (I) may be prepared by method (a) illustrated in
the following scheme and detailed in the experimental section.



In formulas (I), (III) and (IV), R₁, R₂ and p are as defined above.

Compounds of general formula (III) may be prepared from the corresponding secondary amines following the standard method (b) described in literature.

5

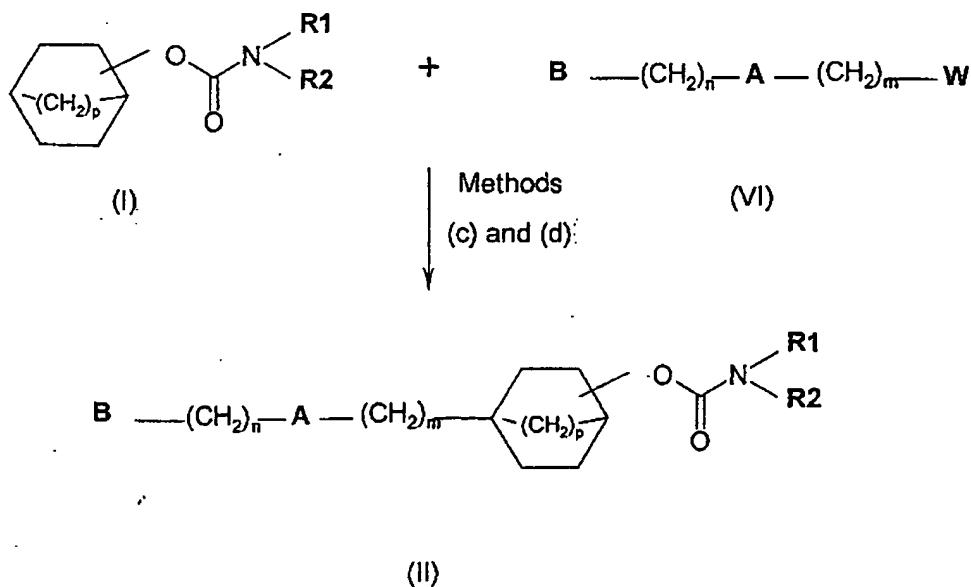


Amines of general formula (V) that are not commercially available have been prepared by synthesis according to standard methods. For example, amines wherein R1 is thiophen-2-ylmethyl and R2 is as defined above, were obtained by reductive alkylation. The corresponding aldehyde is treated with the corresponding primary amine to form the imine, which is reduced with sodium borohydride to obtain the secondary amine.

10 The carbamates of formula (I) may be converted to pharmaceutically acceptable salts by methods known in the art. Typically, a carbamate of formula (I) is treated with an inorganic or organic acid such as fumaric, tartaric, succinic or hydrochloric acid.

15 The quaternary ammonium derivatives of general formula (II), may be prepared by reaction of an alkylating agent of general formula (VI) with compounds of general formula (I). In formulas (I), (II) and (VI), R1, R2, A, B, X, n, m and p are as defined above.

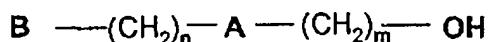
20



In formula (VI), W represents any suitable leaving group, such as a group X as defined above. Preferably, W represents a group X.

This alkylation reaction may be carried out by two different experimental procedures, (c) and (d) which are described below. In particular method (d) provides a new experimental process, using solid phase extraction methodologies that allows the parallel preparation of several compounds. If W represents a group other than X, the quaternary ammonium salt of formula (II) is produced from the product of method (c) or (d) by carrying out an exchange reaction according to standard methods to replace the anion W^- with the desired anion X^- .

Methods (c) and (d) are described in the experimental section. Compounds of general formula (VI) which are not commercially available have been prepared by synthesis according to standard methods. For example, compounds wherein n = 0 and A= -O-, -S- or -NR₄, wherein R₄ is as defined above, were obtained by reaction of the corresponding aromatic derivative or its potassium salt with an alkylating agent of general formula Y-(CH₂)_m-X, wherein X may be a halogen and Y may be a halogen or a sulphonate ester. In other examples, compounds of general formula (VI), where n>=1 were synthesised from the corresponding alcohol derivative of general formula (VII) by known methods.



(VII)

Compounds of formula (IV) could be:

25 4-hydroxy-1-azabicyclo[2.2.1]heptane, described in WO93/15080
4-hydroxy-1-azabicyclo[2.2.2]octane, described in Grob, C.A. et.al. Helv.Chim.Acta (1958), 41, 1184-1190
3(R)-hydroxy-1-azabicyclo[2.2.2]octane or 3(S)-hydroxy-1-azabicyclo[2.2.2]octane, described in Ringdahl, R: Acta Pharm Suec. (1979), 16, 281-283 and commercially
30 available from CU Chemie Uetikon GmbH.

The structures of the prepared compounds were confirmed by ¹H-NMR and MS. The NMR were recorded using a Varian 300 MHz instrument and chemical shifts

are expressed as parts per million (δ) from the internal reference tetramethyl silane. Their purity was determined by HPLC, using reverse phase chromatography on a Waters instrument, with values greater than 95% being obtained. Molecular ions were obtained by electrospray ionization mass spectrometry on a Hewlett Packard instrument. HPLC-MS experiments were performed on a Gilson instrument equipped with a binary pump (Gilson piston pump 321); a vacuum degasser (Gilson 864); an injector-fraction collector (Gilson liquid handler 215); two injection modules, analytical and preparative (Gilson 819); a valve (Gilson Valvemate 7000); a 1/1000 splitter (Acurate by LC Packings); a make-up pump (Gilson 307); a diode array detector (Gilson 170) and a MS detector (a Thermoquest Finnigan aQa, a quadrupole mass spectrometer with ES and APCI ionisation modes). The HPLC-MS instrument was controlled by an IBM PC.

15 **Method (a)**

Example 54 - Preparation of butylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester.

0.65 g (28.50 mmol) of sodium was added to 70 ml of dry toluene. The suspension was refluxed with vigorous stirring. When all the sodium was melted, 3.60 g (28.30 mmol) of (R)-3-hydroxy-1-azabicyclo[2.2.2]octane was added and stirring continued for 2 hours, by which time all the sodium had reacted to form the alcoholate. 6.00 g (28.30 mmol) of Phenylbutylcarbamyl chloride dissolved in 30 ml of toluene was then slowly added. The mixture was refluxed for one hour, and then the reaction was stirred overnight at room temperature. The suspension was filtered and the filtrate evaporated. Ether was added to the residue and stirred for 10 min. The suspension was filtered and the filtrate concentrated in vacuo to obtain 7.18 g of brown oil. This product was purified by column chromatography (silica gel, chloroform/ethanol/ammonia 140:8:1) to yield 1.78 g (5.89 mmol) (22%) of a pure product, structure confirmed by $^1\text{H-NMR}$.

30 300MHz,CDCl₃: δ 0.9 (m, 3H), 1.3 (m, 4H), 1.5 (m, 4H), 1.9 (s, 1H), 2.7 (m, 5H), 3.2 (m, 1H), 3.7 (m, 2H), 4.7 (m, 1H), 7.2-7.4 (m, 5H); MS [M+1]⁺ : 303.

Example 150 - Preparation of cyclopentylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester.

35 0.57 g (24.59 mmol) of sodium was added to 70 ml of dry toluene. The suspension was refluxed with vigorous stirring. When all the sodium was melted, 3.11 g (24.42 mmol) of (R)-3-hydroxy-1-azabicyclo[2.2.2]octane was added and stirred for 2 hours, by which

time all the sodium had reacted to form the alcoholate. 4.96 g (20.35 mmol) of cyclopentylthiophen-2-ylmethylcarbamyl chloride dissolved in 30 ml of toluene was then slowly added. The mixture was refluxed for five hours, and then the reaction was stirred overnight at room temperature. The suspension was filtered and the filtrate 5 washed with water. The organic layer was extracted with 20 % HCl and the aqueous layer basified with 8N NaOH and extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4 anhydride and evaporated. The oil obtained (4.50 g) was purified by column chromatography (silica gel, chloroform/ethanol/ammonia 225:8:1) to obtain 2.25 g (6.73 mmol) (33%) of a pure 10 product, structure confirmed by $^1\text{H-NMR}$.

300MHz, (DMSO-d₆): δ 1,20-1,40 (m, 1H), 1,45-1,72 (m, 11H), 1,89 (bs, 1H), 2,45-2,62 (m, 5H), 3,03-3,10 (m, 1H), 4,22 (bs, 1H), 4,50-4,63 (m, 3H), 6,93-6,99 (m, 2H), 7,38 (m, 1H); MS [M+1]⁺: 335.

15 **Example 159 - Preparation of Benzylphenylcarbamic acid 1-azabicyclo[2.2.1]hept-4-yl ester**

In a two necked flask under nitrogen, 3 ml of THF and 150 mg (1.33 mmoles) of 4-hydroxy-1-azabicyclo[2.2.1]heptane were placed. The suspension was cooled to -60°C and 0.7 ml (1.46 mmoles) of LDA was added dropwise. After the addition the 20 temperature was allowed to rise to 0 °C and was kept during two hours. A solution of 295 mg (1.20 mmoles) of benzylphenylcarbamyl chloride in 2 ml of THF was added in 30 minutes. The reaction mixture was allowed to slowly warm to room temperature and stirred for 18 hours. The suspension was filtered and the filtrate concentrated under reduced pressure. The residue was extracted with dichloromethane and water. The 25 organic layer was extracted with 2N HCl and the aqueous layer basified with 8N NaOH and extracted with dichloromethane. The organic layers were dried over Na_2SO_4 anhydride and evaporated. The oil obtained (162 mg) was purified by HPLC-MS to obtain 4.86 mg (0.015 mmoles) 1.3% of a pure product as formiate, structure confirmed by $^1\text{H-NMR}$.

30 300MHz, (DMSO-d₆): δ 1,86 (m, 4H), 2,65 (s, 2H), 2,77 (bs, 2H), 3,03 (bs, 2H), 4,84 (s, 2H), 7,14-7,32 (m, 10H), 8,19 (s, 1H); MS [M-HCOO]⁺: 323.

Method (b)

35 Carbamoyl chlorides of general formula (III) were prepared according to procedures described in the literature: M. Saraswati et al. Drug Development Research (1994).

31, 142-146; G. M. Shutske et al. J. Heterocycl. Chem. (1990), 27, 1617; GB 1246606; US 2762796.

Example I-1 – Preparation of butylphenylcarbamyl chloride.

- 5 To a solution of 6.72 g (45 mmol) of butylphenylamine in 50 ml of methylene chloride cooled to 10 °C was added slowly with stirring 6.67 g (22.5 mmol) of triphosgene in 40 ml of methylene chloride. The reaction was allowed to continue at room temperature for 27 hours. The solvent was evaporated and the residue extracted twice with n-hexane. The organic solution was concentrated in vacuo to yield 9.11g (43.03 mmol) of
10 a yellow oil (96%). $^1\text{H-NMR}$ (CDCl_3) : δ 0,9 (m, 3H), 1,3 (m, 2H), 1,6 (m, 2H), 3,7 (m, 2H), 7,2-7,4 (m, 5H).

Example I-2 – Preparation of cyclopentylthiophen-2-ylmethylcarbamyl chloride

- To a solution of 5.0 g (27.58 mmol) of cyclopentylthiophen-2-ylmethylamine in 40 ml of
15 methylene chloride at 10 °C was added slowly with stirring 4.09 g (13.79 mmol) of triphosgene in 35 ml of methylene chloride. The reaction was allowed to continue stirring at room temperature for 64 hours, refluxed for 4 hours and 25 hours more at room temperature. The solvent was evaporated and the residue extracted with n-hexane. The organic solution was concentrated to yield 4.96 g (20.34 mmol) of a brown
20 oil (74%). $^1\text{H-NMR}$ (CDCl_3) : δ 1,4 (m, 8H), 4,2 (bs, 1H), 4,5 (m, 2H), 6,8-7,3 (m, 3H).

Method (c)

- Example 146 – Preparation of (R)-3-(bis-thiophen-2-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane, bromide.**
- 25 0.54 g (1.5 mmol) of bis-thiophen-2-ylmethylcarbamic acid-1-azabicyclo[2.2.2]oct-3-(R)yl ester, 7.5 ml of tetrahydrofuran and 0.46 g (2.25 mmol) of 2-(3-bromopropyl)thiophene were mixed. The solution was refluxed for 4 hours and allowed to continue stirring at room temperature for 116 hours. Ether was added and the suspension was stirred for 30 min. The solvent was extracted and more ether was added. This procedure was repeated several times in order to eliminate the alkylating agent. Finally the suspension was filtered and the residue dried in the vacuum oven. The yield was 0.69 g (1.22 mmol) (81%). $^1\text{H-NMR}$ (DMSO-d_6) : 1,78-2,10 (m, 6H), 2,34 (bs, 1H), 2,82 (m, 2H), 3,21-3,46 (m, 7H), 3,89 (m, 1H), 4,54 (m, 4H), 5,06 (m, 1H), 6,95-7,01 (m, 4H), 7,07-7,11 (m, 2H), 7,38-7,49 (m, 3H); MS $[\text{M-Br}]^+$: 487; mp : 35 143 °C.

Method (d)**Example 133 - Preparation of 1-heptyl-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

5 30 mg (0.08 mmols) of phenyl-thiophen-3-yl methyl carbamic acid 1-aza-bicyclo[2.2.2]oct-3-(R)yl ester were dissolved in 1ml of DMSO. To this solution 75 mg (0.40 mmol) of heptyl bromide were added. After stirring overnight at room temperature, the mixture was purified by solid phase extraction with a cation exchange Mega Bond Elut cartridge, previously conditioned at pH = 7.5 with 0.1 M NaH₂PO₄ buffer. The reaction mixture was applied to the cartridge and washed first with 2 ml of DMSO and then three times with 5 ml of CH₃CN, rinsing away all starting materials. The ammonium derivative was eluted with 5 ml of 0.03 M TFA solution in CH₃CN:CHCl₃ (2:1). This solution was neutralized with 300 mg of poly(4-vinylpyridine), filtered and evaporated to dryness.

15 The yield was 12 mg (34%) of title compound. ¹H-NMR (DMSO-d₆): δ 0.88 (m, 3H), 1.28 (m, 8H), 1.60-2.19 (m, 7H), 3.00-3.41 (m, 7H), 3.83 (m, 1H), 4.88 (s, 2H), 5.99 (m, 1H), 7.01 (m, 1H), 7.21-7.39 (m, 6H), 7.49-7.52 (m, 1H); MS [M-CF₃COO]⁺ : 441

20 Also included within the scope of the present invention are pharmaceutical compositions which comprise, as the active ingredient, at least one quinuclidine derivative of general formula (I) or (II) in association with a pharmaceutically acceptable carrier or diluent. Preferably the composition is made up in a form suitable for oral administration.

25 The pharmaceutically acceptable carrier or diluents which are mixed with the active compound or compounds, to form the composition of this invention are well-known *per se* and the actual excipients used depend *inter alia* on the intended method of administration of the composition.

Compositions of this invention are preferably adapted for oral administration. In 30 this case, the composition for oral administration may take the form of tablets, film-coated tablets, liquid inhalant, powder inhalant and inhalation aerosol; all containing one or more compounds of the invention; such preparations may be made by methods well-known in the art.

The diluents which may be used in the preparations of the compositions include 35 those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or film-coated tablets may conveniently contain between 0.1 mg and 500 mg, preferably from 0.5 to 200 mg of

active ingredient. The inhalant compositions may contain between 1 μ g and 1,000 μ g, preferably from 10 to 800 μ g of active ingredient. In human therapy, the dose of the compound of general formula (I) or (II) will depend on the desired effect and duration of treatment; adult doses are generally between 0.5 mg and 300 mg per day as tablets and 10 μ g and 800 μ g per day as inhalant composition.

The compounds of the present invention, or pharmaceutical compositions containing them, may be used together with a β_2 agonist, steroid, antiallergic drug and/or phosphodiesterase IV inhibitor, for simultaneous, separate or sequential use in the treatment of a respiratory disease.

10

Pharmacological Action

The following examples demonstrate the excellent pharmacological activities of the compounds of the present invention. The results on human muscarinic receptor binding and in the test on bronchospasm in guinea pig, were obtained as described below.

Human muscarinic receptor studies.

20 The binding of [3 H]-NMS to human muscarinic receptors was performed according to Waelbroeck et al (1990), Mol. Pharmacol., 38: 267-273. Assays were carried out at 25°C. Membrane preparations from stably transfected chinese hamster ovary-K1 cells (CHO) expressing the genes for the human muscarinic M3 receptors were used.

25 For determination of IC₅₀, membrane preparations were suspended in DPBS to a final concentration of 89 μ g/ml for the M3 subtype. The membrane suspension was incubated with the tritiated compound for 60 min. After incubation the membrane fraction was separated by filtration and the bound radioactivity determined. Non specific binding was determined by addition of 10⁻⁴ M atropine. At least six concentrations were assayed in duplicate to generate individual displacement curves.

Our results (Table 1) show that the compounds of the present invention have high affinities for muscarinic M3 receptors, preferably human muscarinic receptors.

TABLE 1

EXAMPLE N°	BINDING TO RECEPTOR M3 (IC ₅₀ nM)
Atropine	3.2
Ipratropium	3.0
1	5.0
5	11.1
6	18.0
31	8.0
32	8.0
58	8.0
79	14.0
82	4.5
90	9.2
91	6.8
92	11.5
104	19.0
126	8.6
136	9.0
142	17.8
148	14.4
153	6.0
156	18

5 Preferred compounds of the invention have an IC₅₀ (nM) value for M3 receptors of less than 35, preferably less than 25, 20 or 15, more preferably less than 10.

Test on bronchospasm in guinea pig

- The studies were performed according to H. Konzett and F. Rössler (1940),
 10 Arch. Exp. Path. Pharmacol. 195, 71-74. Aqueous solutions of the agents to be tested were nebulized and inhaled by anaesthetized ventilated male guinea pigs (Dunkin-Hartley). Bronchial response to intravenous acetylcholine challenge was determined before and after drug administration and changes in pulmonary resistance at several time-points were expressed as percent of inhibition of bronchospasm..

15

The compounds of the present invention showed bronchodilator activity with high potency and a long duration of action.

From the above described results one of ordinary skill in the art can readily understand that the compounds of the present invention have excellent antimuscarinic

activity (M3) and thus are useful for the treatment of diseases in which the muscarinic M3 receptor is implicated, including respiratory diseases such as chronic obstructive pulmonary disease, bronchitis, asthma, bronchial hyperreactivity and rhinitis; urinary diseases such as urinary incontinence, pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis; gastrointestinal diseases such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulceration; and cardiovascular disorders such as vagally induced sinus bradycardia. For example, the compounds of the present invention are useful for the treatment of respiratory diseases such as chronic obstructive pulmonary disease, chronic bronchitis, asthma, and rhinitis; urinary diseases such as urinary incontinence and pollakiuria in neurinoma, pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis; and gastrointestinal diseases such as irritable bowel syndrome, spastic colitis and diverticulitis.

The present invention further provides a compound of formula (I) or (II) or a pharmaceutically acceptable composition comprising a compound of formula (I) or (II) for use in a method of treatment of the human or animal body by therapy, in particular for the treatment of respiratory, urinary or gastrointestinal disease.

The present invention further provides the use of a compound of formula (I) or (II) or a pharmaceutically acceptable composition comprising a compound of formula (I) or (II) for the manufacture of a medicament for the treatment of respiratory, urinary or gastrointestinal disease.

Further, the compounds of formula (I) or (II) and pharmaceutical compositions comprising a compound of formula (I) or (II) can be used in a method of treating respiratory, urinary or gastrointestinal disease, which method comprises administering to a human or animal patient in need of such treatment an effective amount of a compound of formula (I) or (II) or a pharmaceutical composition comprising a compound of formula (I) or (II).

Further, the compounds of formula (I) and pharmaceutical compositions comprising a compound of formula (I) can be used in combination with other drugs effective in the treatment of these diseases. For example with β_2 agonists, steroids, antiallergic drugs, phosphodiesterase IV inhibitors and/or leukotriene D4 (LTD4) inhibitors, for simultaneous, separate or sequential use in the treatment of a respiratory disease.

The present invention therefore further provides a combination product comprising

- (i) a compound according to the invention; and

- (ii) another compound effective in the treatment of a respiratory, urological or gastrointestinal disease or disorder for simultaneous, separate or sequential use.

The compound (ii) which is effective in the treatment of a respiratory, urological or gastrointestinal disease or disorder may be a β_2 agonist, steroid, antiallergic drug, phosphodiesterase IV inhibitor and/or leukotriene D4 (LTD4) antagonist when the product is for simultaneous, separate or sequential use in the treatment of a respiratory disease. Alternatively, the compound (ii) may be a β_2 agonist, steroid, antiallergic drug and/or phosphodiesterase IV inhibitor when the product is for simultaneous, separate or sequential use in the treatment of a respiratory disease.

The present invention will be further illustrated by the following examples. The examples are given by way of illustration only and are not to be construed as limiting.

15 **Example 1**

Benzylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesised according to method a. The yield of the final step was 1000 mg , 18%. ^1H - NMR (CDCl_3): δ 1,3-1,7 (m, 4H), 1,9 (s, 1H), 2,5-2,8 (m, 5H), 3,2 (m, 1H), 4,8 (m, 1H), 4,9 (s, 2H), 7,1-7,4 (m, 10H); MS $[\text{M}+1]^+$: 337.

20

Example 2

3-(R)(Benzylphenylcarbamoyloxy)-1-methyl-1-azoniabicyclo[2.2.2]octane, trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 20 mg , 34%. ^1H - NMR (DMSO-d_6): δ 1,54-1,90 (m, 4H), 2,17 (s, 1H), 2,95 (s, 3H), 3,22-3,52 (m, 5H), 3,84 (m, 1H), 4,92 (s, 2H), 4,99 (m, 1H), 7,12-7,37 (m, 10H); MS $[\text{M}-\text{CF}_3\text{COO}]^+$: 351.

Example 3

3-(R)(Benzylphenylcarbamoyloxy)-1-(4-methylpent-3-enyl)-1-azoniabicyclo[2.2.2]octane, trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 18 mg , 25%. MS $[\text{M}-\text{CF}_3\text{COO}]^+$: 419.

Example 4**3-(R)(Benzylphenylcarbamoyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step

5 was 21 mg , 26%. ^1H - NMR (DMSO-d₆) : δ 1,56-1,91 (m, 4H), 2,11-2,20 (m, 3H), 3,12 (m, 1H), 3,34-3,51 (m, 6H), 3,86 (m, 1H), 4,06 (m, 2H), 4,93 (s, 2H), 5,02 (m, 1H), 6,97 (m, 3H), 7,20-7,38 (m, 12H); MS [M-CF₃COO]⁺: 471.

Example 5**10 3-(R)(Benzylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane; bromide**

The title compound was synthesised according to method c. The yield of the final step was 220 mg , 70%. ^1H - NMR (DMSO-d₆) : δ 1,55-1,92 (m, 4H), 2,21. (s, 1H), 3,15 (m, 1H), 3,34-3,50 (m, 5H), 3,90 (m, 1H), 4,1 (m, 2 H), 4,02 (s, 2 H), 5,05 (m, 1H), 6,49 (m, 1H), 6,85-6,90 (d, 1H), 7,20-7,59 (m, 12H), 7,59-7,61 (m, 2H); MS [M-Br]⁺: 453; mp :

15 129 °C.

Example 6**20 1-Allyl-3-(R)(benzylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide**

The title compound was synthesised according to method c. The yield of the final step was 230 mg , 85%. ^1H - NMR (DMSO-d₆): δ 1,58-1,91 (m, 4H), 2,20 (s, 1H), 3,10 (m, 1H), 3,27-3,41 (m, 4H), 3,79-3,90 (m, 3H), 4,92 (s, 2H), 5,03 (m, 1H), 5,61 (m, 2H), 5,98 (m, 1H), 7,20-7,38 (m, 10H); MS [M-Br]⁺: 377; mp : 70 °C.

25

Example 7**3-(R)(Benzylphenylcarbamoyloxy)-1-(2-hydroxyethyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 12 mg , 19%. MS [M-CF₃COO]⁺: 381.

Example 8**3-(R)(Benzylphenylcarbamoyloxy)-1-isopropyl-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

35 The title compound was synthesised according to method d. The yield of the final step was 17 mg , 26%. ^1H - NMR (DMSO-d₆): δ 1,24 (m, 6H), 1,64-1,89 (m, 4H), 2,20 (s,1H),

2,78 (m,1H), 3,23-3,32 (m,4 H), 3,50 (m, 1H), 3,76 (m, 1H), 4,92 (s, 2H), 5,06 (m, 1H),
7,20-7,38 (m,10H); MS [M-CF₃COO]⁺: 379.

Example 9

- 5 **3-(R)(Benzylphenylcarbamoyloxy)-1-propyl-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 16 mg , 25%. ¹H- NMR (DMSO-d₆) : δ 0,88 (m, 3H), 1,57-1,68 (m, 4H), 1,89 (m, 2H), 2,18 (s, 1H), 2,99-3,14 (m, 3H), 3,26-3,40 (m, 4H), 3,83 (m,1H), 4,92 (s, 2H), 5,01
10 (m, 1H), 7,20-7,37 (m, 10H); MS [M-CF₃COO]⁺: 379.

Example 10

- 3-(R)(Benzylphenylcarbamoyloxy)-1-(3-cyanopropyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

15 The title compound was synthesised according to method d. The yield of the final step was 13 mg , 19%. ¹H- NMR (DMSO-d₆) : δ 1,67-2,07 (m, 6H), 2,19 (s, 1H), 2,60 (m,2H), 3,07 (m, 1H), 3,21-3,48 (m, 6H), 3,85 (m,1H), 4,92 (s, 2H), 5,01 (m,1H), 7,20-7,37 (m, 10); MS [M-CF₃COO]⁺: 404.

20 **Example 11**

- 3-(R)(Benzylphenylcarbamoyloxy)-1-cyclopropylmethyl-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 9 mg , 14%. MS [M-CF₃COO]⁺: 391.

25

Example 12

- 3-(R)(Benzylphenylcarbamoyloxy)-1-(2-ethoxyethyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 22 mg , 32%. ¹H- NMR (DMSO-d₆) : δ 1,12 (m, 3H), 1,58-1,90 (m, 4H), 2,19 (s, 1H), 3,12-3,15 (m,1H), 3,28-3,53 (m, 8H), 3,75 (m, 2H), 3,90 (m,1H), 4,91 (s, 2H), 5,02 (m,1H), 7,20-7,37 (m, 10H); MS [M-CF₃COO]⁺: 409.

Example 13

- 35 **3-(R)(Benzylphenylcarbamoyloxy)-1-(4-ethoxycarbonylbutyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 14 mg , 18%. ^1H - NMR (DMSO-d₆) : δ 1,19 (m, 3H), 1,50-1,67 (m, 4H), 1,85-1,88 (m, 2H), 2,18 (s, 1H), 2,38 (m, 2H), 3,99 (m, 1H), 3,16-3,42 (m, 8H), 3,82 (m, 1H), 4,06 (m, 2H), 4,92 (s, 2H), 5,02 (m, 1H), 7,19-7,37 (m, 10H); MS [M-CF₃COO]⁺: 465.

5

Example 14

3-(R)(Benzylphenylcarbamoyloxy)-1-(4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 14 mg , 18%. ^1H - NMR (DMSO-d₆) : δ 1,57-1,65 (m, 6H), 1,88 (m, 2H), 2,18 (s, 1H), 2,63 (m, 2H), 3,00 (m, 1H), 3,18-3,42 (m, 6H), 3,79-3,86 (m, 1H), 4,94 (s, 2H), 5,00 (m, 1H), 7,18-7,37 (m, 15H); MS [M-CF₃COO]⁺: 469.

10

Example 15

15 3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(4-fluorophenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 21 mg ; 25%. ^1H - NMR (DMSO-d₆) : δ 1,55-1,91 (m, 4H), 2,10-2,20 (m, 3H), 3,10 (m, 1H), 3,28-3,50 (m, 6H), 3,88 (m, 1H), 4,02 (m, 2H), 4,93 (s, 2H), 5,02 (m, 1H), 6,95-7,12 (m, 2H), 7,12-7,38 (m, 12H); MS [M-CF₃COO]⁺: 489.

20

Example 16

3-(R)(Benzylphenylcarbamoyloxy)-1-(3-hydroxypropyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

25 The title compound was synthesised according to method d. The yield of the final step was 12 mg , 18%. ^1H - NMR (DMSO-d₆) : δ 1,54-1,88 (m, 6H), 2,18 (s, 1H), 3,09 (m, 1H), 3,23-3,49 (m, 8H), 3,85 (m, 1H), 4,84 (m, OH), 4,92 (s, 2H), 5,02 (m, 1H), 7,19-7,37 (m, 10H); MS [M-CF₃COO]⁺: 395.

30

Example 17

1-(4-Acetoxybutyl)-3-(R)(benzylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

35 The title compound was synthesised according to method d. The yield of the final step was 9 mg , 12%. ^1H - NMR (DMSO-d₆) : δ 1,40-1,70 (m, 5H), 1,81-1,91 (m, 3H), 2,02 (m, 3H), 2,19 (s, 1H), 3,03 (m, 1H), 3,19 (m, 2H), 3,26-3,46 (m, 4H); 3,80-3,84 (m, 1H), 4,04 (m, 2H), 4,92 (s, 2H), 5,01-5,02 (m, 1H), 7,19-7,37 (m, 10H); MS [M-CF₃COO]⁺: 451.

Example 18**3-(R)(Benzylphenylcarbamoyloxy)-1-(4-oxo-4-thiophen-2-ylbutyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

- 5 The title compound was synthesised according to method d. The yield of the final step was 16 mg , 19%. ^1H - NMR (DMSO-d₆) : δ 1,55-1,69 (m, 2H), 1,87-2,05 (m, 4H), 2,19 (s, 1H), 3,09 (m, 3H), 3,22 (m, 2H), 3,29-3,46 (m, 4H), 3,88 (m, 1H), 4,93 (s, 2H), 5,02 (m, 1H), 7,19-7,38 (m, 11H), 7,98-8,06 (m, 2H); MS [M-CF₃COO]⁺: 489.

10 Example 19**3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(3-hydroxyphenoxy)propyl]-1-azonia bicyclo[2.2.2]octane; trifluoroacetate**

- The title compound was synthesised according to method d. The yield of the final step was 17 mg , 21%. ^1H - NMR (DMSO-d₆) : δ 1,57-1,68 (m, 2H), 1,90 (m, 2H), 2,08-2,19 (m, 3H), 3,11 (m, 1H), 3,28-3,50 (m, 6H), 3,88 (m, 1H), 3,97 (m, 2H), 4,93 (s, 2H), 5,02 (m, 1H), 6,33-6,40 (m, 3H), 7,04 (m, 1H), 7,20-7,38 (m, 10H), 9,5 (s, OH); MS [M-CF₃COO]⁺: 487.

Example 20

- 20 **3-(R)(Benzylphenylcarbamoyloxy)-1-heptyl-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 17 mg , 23%. ^1H - NMR (DMSO-d₆) : δ 0,88 (m, 3H), 1,28 (m, 8H), 1,62 (m, 4H), 1,85-1,88 (m, 2H), 2,18 (s, 1H), 3,02 (m, 1H), 3,15 (m, 2H), 3,26-3,40 (m, 4H), 3,83 (m, 1H), 4,92 (s, 2H), 5,01 (m, 1H), 7,20-7,37 (m, 10H); MS [M-CF₃COO]⁺: 435.

Example 21**1-(2-Benzyloxyethyl)-3-(R)(benzylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

- 30 The title compound was synthesised according to method d. The yield of the final step was 20-mg , 25%. ^1H - NMR (DMSO-d₆) : δ 1,54-1,94 (m, 4H), 2,20 (s, 1H), 3,17 (m, 1H), 3,28-3,55 (m, 6H), 3,85 (m, 2H), 9,92-3,99 (m, 1H), 4,53 (s, 2H), 4,91 (s, 2H), 5,02 (m, 1H), 7,18-7,40 (m, 15H); MS [M-CF₃COO]⁺: 471.

Example 22**Benzyl-(4-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester**

The title compound was synthesised according to method a. The yield of the final step
5 was 1110 mg , 13%. ^1H - NMR (DMSO-d₆) : δ 1,16-1,52 (m, 4H), 1,81 (s, 1H), 2,42-
2,57 (m, 5H), 2,99-3,07 (m, 1H), 4,63 (m, 1H), 4,84 (s, 2H), 7,10-7,32 (m, 9H); MS
[M+1] : 355.

Example 23**10 1-Allyl-3-(R)[benzyl-(4-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane;
trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 10 mg , 23%. MS [M-CF₃COO]⁺: 395.

15 Example 24**3-(R)[Benzyl-(4-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo
[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 13 mg , 25%. MS [M-CF₃COO]⁺: 473.

20

Example 25**Benzyl-p-tolylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester**

The title compound was synthesised according to method a. The yield of the final step
was 1070 mg , 11%. ^1H - NMR (DMSO-d₆) : δ 1,18-1,30 (m, 2H), 1,45-1,55 (m, 2H),

25 1,83 (s, 1H), 2,25 (s, 3H), 2,43-2,59 (m, 5H), 3,01-3,10 (m, 1H), 4,64 (m, 1H), 4,85 (s,
2H), 7,12-7,34 (m, 9H); MS [M+1]⁺ : 351.

Example 26**1-Allyl-3-(R)(benzyl-p-tolyl-carbamoyloxy)-1-azoniabicyclo[2.2.2]octane;**

30 **trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 9 mg , 19%. MS [M-CF₃COO]⁺: 391.

Example 27**35 3-(R)(Benzyl-p-tolylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]
octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 13 mg , 25%. MS [M- CF₃COO]⁺: 469.

Example 28

5 **3-(R)(Benzylphenylcarbamoyloxy)-1-[2-(2-methoxyethoxy)ethyl]-1-azoniabicyclo[2.2.2]octane; bromide**

The title compound was synthesised according to method c. The yield of the final step was 390 mg , 84%. ¹H- NMR (DMSO-d₆) : δ 1,55-1,75 (m, 2H), 1,88 (m, 2H), 2,17 (s, 1H), 3,14 (m, 1H), 3,22 (s, 3H), 3,29-3,55 (m, 10H), 3,78 (m, 2H), 3,90 (m, 1H), 4,89 (s, 2H), 4,99 (m, 1H), 7,17-7,35 (m, 10H); MS [M-Br]⁺: 439.

Example 29

3-(R)(Benzylphenylcarbamoyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane;
bromide

15 The title compound was synthesised according to method c. The yield of the final step was 200 mg , 65%. ¹H- NMR (DMSO-d₆) : δ 1,55-1,75 (m, 2H), 1,90 (m, 2H), 2,19 (s, 1H), 3,00 (m, 2H), 3,10 (m, 1H), 3,31-3,51 (m, 6H), 3,90 (m, 1H), 4,91 (s, 2H), 5,04 (m, 1H), 7,18-7,37 (m, 15H). MS [M-Br]⁺: 441; mp 81 °C.

20 **Example 30**

3-(R)(Benzylphenylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide

The title compound was synthesised according to method c. The yield of the final step was 970 mg , 82%. ¹H- NMR (DMSO-d₆) : δ 1,55-1,69 (m, 2H), 1,85-2,04 (m, 4H), 2,18 (s, 1H), 2,83 (m, 2H), 3,01 (m, 1H), 3,20-3,44 (m, 6H), 3,85 (m, 1H), 4,92 (s, 2H), 5,00 (m, 1H), 6,94-7,00 (m, 2 H), 7,19-7,40 (m, 11H). MS [M-Br]⁺: 461; mp 95 °C.

Example 31

3-(R)(Benzylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide

The title compound was synthesised according to method c. The yield of the final step was 880 mg , 79%. ¹H- NMR (DMSO-d₆) : δ 1,55-1,69 (m, 2H), 1,85-2,00 (m, 4H), 2,18 (s, 1H), 2,59 (m, 2H), 3,04 (m, 1H), 3,23-3,44 (m, 6H), 3,85 (m , 1H), 4,92 (s, 2H), 5,02 (m, 1H), 7,18-7,36 (m, 15H). MS [M-Br]⁺: 455; mp 101 °C.

Example 32**3-(R)(Benzylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide**

The title compound was synthesised according to method c. The yield of the final step
5 was 360 mg , 67%. ^1H - NMR (DMSO-d₆) : δ 1,5-1,73 (m, 2H), 1,89 (m, 2H), 2,20 (s,
1H), 3,23 (m, 1H), 3,46-3,72 (m, 6H), 4,02 (m, 1H), 4,43 (m, 2H), 4,92 (s, 2H), 5,03 (m,
1H), 7,01 (m, 3H), 7,17-7,38 (m, 12H); MS [M-Br]⁺: 457; mp 117 °C.

Example 33**10 3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(3-cyanophenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 16 mg ; 36%; MS [M- CF₃COO]⁺: 496.

15 Example 34**3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(naphthalen-1-yloxy)propyl]-1-azonia
bicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 10 mg , 21%; MS [M- CF₃COO]⁺: 521.

20

Example 35**3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(methylphenylamino)propyl]-1-azonia
bicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
25 was 12 mg , 28%; MS [M- CF₃COO]⁺: 484.

Example 36**3-(R)(Benzylphenylcarbamoyloxy)-1-(3-phenylsulfanylpropyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

30 The title compound was synthesised according to method d. The yield of the final step
was 8 mg , 18%; ^1H - NMR (DMSO-d₆) : δ 1,45-2,00 (m, 6H), 2,17 (bs, 1H), 3,00 (m,
2H), 3,28-3,41 (m, 7H), 3,83 (m, 1H), 4,91 (s, 2H), 4,98 (m, 1H), 7,18-7,41 (m, 15H);
MS [M- CF₃COO]⁺: 487.

35 Example 37**3-(R)(Benzylphenylcarbamoyloxy)-1-(4-oxo-4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 10 mg , 23%; ¹H- NMR (DMSO-d₆) : δ 1,50-2,06 (m, 6H), 2,20 (bs, 1H), 3,13-3,47 (m, 9H), 3,89 (m, 1H), 4,93 (s, 2H), 5,02 (m, 1H), 7,19-7,38 (m, 10H), 7,54-7,70 (m, 3H), 7,98-8,00 (m, 2H); MS [M- CF₃COO]⁺: 483.

5

Example 38**3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(2,4,6-trimethylphenoxy)propyl]-1-azonia bicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 14 mg , 30%; ¹H- NMR (DMSO-d₆) : δ 1,50-2,20 (m, 7H), 2,19 (s, 9H), 3,16-3,52 (m, 7H), 3,73 (m, 2H), 3,92 (m, 1H), 4,93 (s, 2H), 5,03 (m, 1H), 6,83 (s, 2H), 7,19-7,38 (m, 10H); MS [M- CF₃COO]⁺: 513.

Example 39**15 3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(2-chlorophenoxy)propyl]-1-azoniabicyclo [2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 14 mg , 31%; MS [M- CF₃COO]⁺: 506.

20 Example 40**3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(3-trifluoromethylphenoxy)propyl]-1- azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 14 mg , 29%; ¹H- NMR (DMSO-d₆) : δ 1,50-2,00 (m, 4H), 2,08-2,20 (m, 3H), 3,12- 3,50 (m, 7H), 3,90 (m, 1H), 4,14 (m, 2H), 4,93 (s, 2H), 5,03 (m, 1H), 7,19-7,38 (m, 13H), 7,54-7,59 (m, 1H). MS [M- CF₃COO]⁺: 539.

Example 41**30 3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(biphenyl-4-yloxy)propyl]-1-azoniabicyclo [2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 12 mg , 24%; ¹H- NMR (DMSO-d₆) : δ 1,50-2,20 (m, 7H), 3,14 (bs, 1H), 3,28-3,52 (m, 6 H), 3,91 (m, 1H), 4,10 (m, 2H), 4,93 (s, 2H), 5,03 (m, 1H), 7,03-7,08 (m, 2H), 7,18-7,47 (m,13H), 7,61-7,65 (m, 4H); MS [M- CF₃COO]⁺: 547.

Example 42**3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(2,4-difluorophenoxy)propyl]-1-azonia
bicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
5 was 10 mg , 22%; ¹H- NMR (DMSO-d₆) : δ 1,50-2,19 (m, 7H), 3,10 (bs, 1H), 3,28-3,51
(m,6H), 3,90 (m, 1H), 4,10 (m, 2H), 4,93 (s, 2H), 5,02 (m, 1H), 7,02-7,09 (m, 1H), 7,19-
7,37 (m, 12H); MS [M- CF₃COO]⁺: 507.

Example 43**10 3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(4-methoxyphenoxy)propyl]-1-azonia
bicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 10 mg , 22%; ¹H- NMR (DMSO-d₆) : 1,50-2,19 (m, 7H), 3,11 (bs, 1H), 3,28-3,51
(m, 6H), 3,70 (s,3H), 3,89 (m, 1H), 3,94-3,99 (m, 2H), 4,93 (s, 2H), 5,02 (m, 1H), 6,85-
15 6,92 (m, 4H), 7,19-7,38 (m, 10H); MS [M- CF₃COO]⁺: 501.

Example 44**3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)
propyl]-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

20 The title compound was synthesised according to method d. The yield of the final step
was 10 mg , 21%; ¹H- NMR (DMSO-d₆) : δ 1,50-1,71 (m, 6H), 1,87-2,19 (m, 5H), 2,63-
2,68 (m, 4H), 3,10 (bs, 1H), 3,28-3,50 (m, 6H), 3,88 (m, 1H), 3,98 (m, 2H), 4,93 (s, 2H),
5,02 (m, 1H), 6,63-6,70 (m, 2H), 6,95-6,98 (d, 1H), 7,19-7,38 (m, 10H); MS [M-
CF₃COO]⁺: 525.

25 Example 45**1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-3-(R)(benzylphenylcarbamoyloxy)-1-azonia
bicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
30 was 12 mg , 26%; MS [M- CF₃COO]⁺: 515.

Example 46**3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(2-carbamoylphenoxy)propyl]-1-azonia
bicyclo[2.2.2]octane; trifluoroacetate**

35 The title compound was synthesised according to method d. The yield of the final step
was 10 mg , 22%; ¹H- NMR (DMSO-d₆) : δ 1,50-2,27 (m, 7H), 3,09 (bs, 1H), 3,28-3,48
(m, 6H), 3,88 (m, 1H), 4,14 (m, 2H), 4,93 (s, 2H), 5,04 (m, 1H), 7,02-7,15 (m, 2H), 7,19-

7,38 (m, 10H), 7,44-7,50 (m, 1H), 7,55(bs, NH₂), 7,69-7,72 (dd, 1H); MS [M-CF₃COO]⁺: 514.

Example 47

- 5 **3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(3-dimethylaminophenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 12 mg , 26%; MS [M- CF₃COO]⁺: 514.

10 **Example 48:**

- .1-[3-(4-Acetylaminophenoxy)propyl]-3-(R)(benzylphenylcarbamoyloxy)-1-azonia:bicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 12 mg , 25%; ¹H- NMR (DMSO-d₆) : δ 1,50-1,92 (m, 4H), 2,01 (s, 3H), 2,04-2,20 (m, 3H), 3,12 (bs, 1H), 3,28-3,51 (m, 6H), 3,89 (m, 1H), 4,00 (m, 2H), 4,93 (s, 2H), 5,02 (m, 1H), 6,86-6,91 (m, 2H), 7,19-7,38 (m, 10H), 7,48-7,53 (m. 2H), 9,85 (s,NH); MS [M- CF₃COO]⁺: 528.

Example 49

- 20 **3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(4-methoxycarbonylphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 12 mg , 25%; ¹H- NMR (DMSO-d₆) : δ 1,50-2,20 (m, 7H), 3,12 (bs, 1H), 3,29-3,51 (m, 6H), 3,82 (s, 3H), 3,87-3,93 (m, 1H), 4,14 (m, 2H), 4,93 (s, 2H), 5,03(m, 1H), 7,04-7,09 (m, 2H), 7,19-7,38 (m, 10H), 7,92-7,96 (m, 2H); MS [M- CF₃COO]⁺: 529.

Example 50

- 30 **3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(4-nitrophenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 12 mg , 26%; ¹H- NMR (DMSO-d₆) : δ 1,50-2,27 (m, 7H), 3,12 (bs, 1H), 3,29-3,51 (m, 6H), 3,87-3,94 (m, 1H), 4,21 (m, 2H), 4,93 (s, 2H), 5,03 (m, 1H), 7,14-7,38 (m, 12H), 8,22-8,28 (m, 2H); MS [M- CF₃COO]⁺: 516.

35 **Example 51**

- 3-(R)(Benzylphenylcarbamoyloxy)-1-[3-(4-hydroxymethylphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 10 mg , 22%; MS [M- CF₃COO]⁺: 501.

Example 52

5 **Benzylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(S)yl ester**

The title compound was synthesised according to method a. The yield of the final step was 1000 mg , 23%; ¹H- NMR (DMSO-d₆) : δ 1,14-1,57 (m, 4H), 1,83 (bs, 1H), 2,43-2,61 (m, 5H), 2,61 -3,01 (m, 1H), 4,64 (m, 1H), 4,89 (s, 2H), 7,16-7,35 (m, 10H).MS [M+1]⁺ : 337.

10

Example 53

3-(S)(Benzylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide

15

The title compound was synthesised according to method c. The yield of the final step was 660 mg , 83%.¹H- NMR (DMSO-d₆) : δ 1,40-2,00 (m, 6H), 2,18 (bs, 1H), 2,59 (m, 2H), 2,95-3,44 (m, 7H), 3,84 (m, 1H), 4,92 (s, 2H), 5,00 (m, 1H), 7,19-7,36 (m, 15H).MS [M- Br]⁺: 455; mp : 64 °C.

Example 54

20 **Butylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester**

The title compound was synthesised according to method a. The yield of the final step was 1880 mg , 22%;¹H- NMR (CDCl₃) : δ 0,9 (m, 3H), 1,3 (m, 4H), 1,5 (m, 4H), 1,9 (s, 1H), 2,7 (m, 5H), 3,2 (m, 1H), 3,7 (m, 2H), 4,7 (m, 1H), 7,2-7,4 (m, 5H);MS [M+1]⁺ : 303.

25

Example 55

3-(R)(Butylphenylcarbamoyloxy)-1-methyl-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

30

The title compound was synthesised according to method d. The yield of the final step was 16 mg , 30%; MS [M- CF₃COO]⁺: 317.

Example 56

3-(R)(Butylphenylcarbamoyloxy)-1-(4-methylpent-3-enyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

35

The title compound was synthesised according to method d. The yield of the final step was 18 mg , 27%; MS [M- CF₃COO]⁺: 385.

Example 57

3-(R)(Butylphenylcarbamoyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
5 was 21 mg , 28%; MS [M- CF₃COO]⁺: 437.

Example 58

3-(R)(Butylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane; bromide

10 The title compound was synthesised according to method c. The yield of the final step
was 182 mg , 48%; ¹H- NMR (DMSO-d₆) : δ 0,84 (m, 3H), 1,25 (m, 2H), 1,40 (m, 2H),
1,70-1,91 (m, 4H), 2,20 (s, 1H), 3,2-3,4 (m, 6 H), 3,64 (m, 2H), 3,88 (m, 1H), 3,88-4,07
(d, 2H), 4,97 (m, 1H), 6,45 (m, 1H), 6,83-6,88 (d, 1H), 7,23-7,45 (m, 7H), 7,60 (m, 2H);
MS [M- Br]⁺: 419; mp : 144 °C

15

Example 59

1-Allyl-3-(R)(butylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide

The title compound was synthesised according to method c. The yield of the final step
was 200 mg , 72%; ¹H- NMR (DMSO-d₆) : δ 0,85 (m, 3H), 1,21-1,34 (m, 3H), 1,40-1,45
(m, 2H), 1,70-2,18 (m, 4H), 3,15-3,40 (m, 5H), 3,61-3,67 (m, 2H), 3,82 (m, 1H), 3,92-
3,94 (m, 2H), 4,95 (m, 1H), 5,62 (m, 2H), 5,97-6,01 (m, 1H), 7,26-7,44 (m, 5H); MS [M-
Br]⁺: 343; mp : 141 °C.

Example 60

25 **3(R)(Butylphenylcarbamoyloxy)-1-(2-hydroxyethyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 13 mg , 19%; MS [M- CF₃COO]⁺: 347.

30 **Example 61**

3-(R)(Butylphenylcarbamoyloxy)-1-isopropyl-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
was 20 mg , 29%; MS [M- CF₃COO]⁺: 345.

35

Example 62

3-(R)(Butylphenylcarbamoyloxy)-1-propyl-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
5 was 16 mg , 23%; MS [M- CF₃COO]⁺: 345.

Example 63

3-(R)(Butylphenylcarbamoyloxy)-1-(3-cyanopropyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

10 The title compound was synthesised according to method d. The yield of the final step
was 15 mg , 20%; MS [M- CF₃COO]⁺: 370.

Example 64

3-(R)(Butylphenylcarbamoyloxy)-1-cyclopropylmethyl-1-azoniabicyclo[2.2.2]

15 **octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 2 mg , 3%; MS [M- CF₃COO]⁺: 357.

Example 65

20 **3-(R)(Butylphenylcarbamoyloxy)-1-(2-ethoxyethyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 19 mg , 25%; MS [M- CF₃COO]⁺: 375.

25 **Example 66**

3-(R)(Butylphenylcarbamoyloxy)-1-(4-ethoxycarbonylbutyl)-1-azoniabicyclo[2.2.2]

octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
was 12 mg , 14%; MS [M- CF₃COO]⁺: 431.

30

Example 67

3-(R)(Butylphenylcarbamoyloxy)-1-(3-hydroxypropyl)-1-azoniabicyclo[2.2.2]

octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
35 was 12 mg , 17%; MS [M- CF₃COO]⁺: 361.

Example 68

3-(R)(Butylphenylcarbamoyloxy)-1-(3-pyrrol-1-ylpropyl)-1-azoniabicyclo[2.2.2]

octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 19 mg, 23%; MS [M- CF₃COO]⁺: 410.

Example 69

- 5 **1-(4-Acetoxybutyl)-3-(R)(butylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 10 mg, 12%; MS [M- CF₃COO]⁺: 417.

- 10 **Example 70**

- 3-(R)(Butylphenylcarbamoyloxy)-1-(4-oxo-4-thiophen-2-ylbutyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 17 mg, 19%; MS [M- CF₃COO]⁺: 455.

- 15 **Example 71**

- 3-(R)(Butylphenylcarbamoyloxy)-1-(4-phenylbutyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 17 mg, 20%; MS [M- CF₃COO]⁺: 435.

Example 72

- 3-(R)(Butylphenylcarbamoyloxy)-1-[3-(3-hydroxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

25 The title compound was synthesised according to method d. The yield of the final step was 21 mg, 23%; MS [M- CF₃COO]⁺: 453.

Example 73

- 3-(R)(Butylphenylcarbamoyloxy)-1-heptyl-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 17 mg, 21%; MS [M- CF₃COO]⁺: 401.

Example 74

- 35 **1-(2-Benzylxyethyl)-3-(R)(butylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 22 mg, 25%; MS [M- CF₃COO]⁺: 437.

Example 75**3-(R)(Butylphenylcarbamoyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane; bromide**

The title compound was synthesised according to method c. The yield of the final step
5 was 330 mg , 82%; ^1H - NMR (DMSO-d₆) : δ 0,83 (m, 3H), 1,27-1,34 (m, 2H), 1,41-1,48
(m, 3H), 1,60-2,23 (m, 4H), 2,96-3,47 (m, 7H), 3,57-3,71 (m, 4H), 3,92 (m, 1H), 4,98
(m, 1H), 7,25-7,45 (m, 10H); MS [M- Br]⁺: 407; mp : 139 °C

Example 76**10 3-(R)(Butylphenylcarbamoyloxy)-1-[2-(2-methoxyethoxy)ethyl]-1-azoniabicyclo
[2.2.2]octane; bromide**

The title compound was synthesised according to method c. The yield of the final step
was 520 mg , 81%; ^1H - NMR (DMSO-d₆) : δ 0,82 (m, 3H), 1,24-1,31 (m, 2H), 1,39-1,47
(m, 2H), 1,70-2,20 (m, 5 H), 3,26 (s, 3H), 3,35-3,70 (m, 13H), 3,82-3,86 (m, 3H), 4,94
15 (m, 1H), 7,26-7,44 (m, 5 H); MS [M- Br]⁺: 405.

Example 77**Butyl-(4-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester**

The title compound was synthesised according to method a. The yield of the final step
20 was 1650 mg , 24%; ^1H - NMR (DMSO-d₆) : δ 0,82 (m, 3H), 1,20-1,54 (m, 8H), 1,83 (m,
1H), 2,49-2,70 (m, 5H), 3,02-3,09 (m, 1H), 3,36-3,63 (m, 2H), 4,59 (m, 1H), 7,19-7,35
(m, 4H). ; MS [M+1]⁺ : 321.

Example 78**25 3-(R)(Butylphenylcarbamoyloxy)-1-[3-(4-fluorophenoxy)propyl]-1-azoniabicyclo
[2.2.2]octane; chloride**

The title compound was synthesised according to method c. The yield of the final step
was 390 mg , 75%; ^1H - NMR (DMSO-d₆) : δ 0,82 (m, 3H), 1,26-1,31 (m, 2H), 1,40-1,48
(m, 2H), 1,70-2,17 (m, 5H), 3,20-3,7 (m, 11H), 3,86 (m, 1H), 4,02 (m, 2H), 4,94 (m, 1H),
30 6,95-7,00 (m, 2H), 7,12-7,18 (m, 2H), 7,26-7,44 (m, 5H); MS [M- Cl]⁺: 455; mp: 126 °C.

Example 79**3-(R)(Butylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]
octane; bromide**

35 The title compound was synthesised according to method c. The yield of the final step
was 260 mg , 53%; ^1H - NMR (DMSO-d₆) : δ 0,84 (m, 3H), 1,23-1,30 (m, 2H), 1,39-1,48
(m, 2H), 1,70-2,20 (m, 5H), 3,20-3,72 (m, 9H), 3,99 (m, 1H), 4,44 (m, 2H), 4,95 (m,
1H), 7,01 (m, 3H), 7,24-7,40 (m, 7H); MS [M- Br]⁺: 423; mp : 153 °C.

Example 80**3-(R)(Butylphenylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide**

5 The title compound was synthesised according to method c. The yield of the final step was 1100 mg , 62%; ^1H - NMR (DMSO-d₆) : δ 0,84 (m, 3H), 1,24-1,31 (m, 2H), 1,42 (m, 2H), 1,60-2,21 (m, 7H), 2,85 (m, 2H), 3,0-3,50 (m, 7H), 3,60-3,69 (m, 2H), 3,85 (m, 1H), 4,93 (m, 1H), 6,95-7,00 (m, 2H), 7,28-7,43 (m, 6H); MS [M- Br]⁺: 427; mp: 127 °C.

10 Example 81**3-(R)(Butylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide**

The title compound was synthesised according to method c. The yield of the final step was 280 mg , 56%; ^1H - NMR (DMSO-d₆) : δ 0,84 (m, 3H), 1,23-1,33 (m, 2H), 1,43 (m, 2H), 1,60-2,20 (m, 7H), 2,59 (m, 2H), 3,00-3,78 (m, 9H), 3,84 (m, 1H), 4,92 (m, 1H), 7,20-7,42 (m, 10H); MS [M- Br]⁺: 421; mp : 120 °C.

Example 82**Phenylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester**

20 The title compound was synthesised according to method a. The yield of the final step was 310 mg , 10%; ^1H - NMR (DMSO-d₆) : δ 1,10-1,60 (m, 4 H), 1,87 (s, 1H), 2,46-2,63 (m, 5H), 3,04-3,33 (m, 1H), 4,66 (m, 1H), 5,01 (s, 2H), 6,87-6,94 (m, 2H), 7,20-7,43 (m, 6H); MS [M+1]⁺ : 343.

25 Example 83**1-Methyl-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide**

The title compound was synthesised according to method c. The yield of the final step was 160 mg , 80%; ^1H - NMR (DMSO-d₆) : 1,65-2,00 (m, 4H), 2,20 (s, 1 H), 2,98 (s, 3H), 3,32-3,52 (m, 5H), 3,85-3,92 (m, 1H), 4,98-5,04 (m, 3H), 6,94 (m, 2H), 7,24-7,45 (m, 6H); MS [M- Br]⁺: 357.

Example 84**1-(3-Phenoxypropyl)-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azonia****bicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 16 mg , 42%; MS [M- CF₃COO]⁺: 477.

Example 85**1-(3-Phenylpropyl)-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azonia
bicyclo[2.2.2]octane; trifluoroacetate**

5 The title compound was synthesised according to method d. The yield of the final step was 13 mg , 35%; ^1H - NMR (DMSO-d₆) : δ 1,72-2,3 (m, 7H), 2,58 (m, 2H), 3,00-3,48 (m, 7H), 3,84 (m, 1H), 5,04 (m, 3H), 6,92-6,94 (m, 2H), 7,20-7,43 (m, 11H); MS [M- CF₃COO]⁺: 461.

10 **Example 86**

**1-(3-Phenylallyl)-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo
[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 4 mg , 11%; MS [M- CF₃COO]⁺: 459.

15

Example 87**1-(2-Benzylxyethyl)-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azonia
bicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 14 mg , 37%; MS [M- CF₃COO]⁺: 477.

Example 88**1-[3-(3-Hydroxyphenoxy)propyl]-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-
1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

25 The title compound was synthesised according to method d. The yield of the final step was 11 mg , 28%; MS [M- CF₃COO]⁺: 493.

Example 89**1-Heptyl-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]
octane; trifluoroacetate**

30 The title compound was synthesised according to method d. The yield of the final step was 13 mg , 37%; MS [M- CF₃COO]⁺: 441.

Example 90**3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-
azoniabicyclo[2.2.2]octane; bromide**

The title compound was synthesised according to method c. The yield of the final step was 140 mg , 48%; ^1H - NMR (DMSO-d₆) : δ 1,40-2,30 (m, 7H), 2,83 (m, 2H), 3,00-3,60 (m, 7H), 3,88 (m, 1H), 5,04 (m, 3H), 6,93-6,99 (m, 4H), 7,28-7,43 (m, 7H); MS [M- Br]⁺: 467.

5

Example 91**1-(2-Phenoxyethyl)-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azonia bicyclo[2.2.2]octane; bromide**

The title compound was synthesised according to method c. The yield of the final step was 510 mg , 80%; ^1H - NMR (DMSO-d₆) : δ 1,40-2,30 (m, 5H), 3,20-3,73 (m, 7H), 4,05 (m, 1H), 4,44 (bs, 2H), 5,04 (m, 3H), 6,91-7,04 (m, 5H), 7,24-7,41 (m, 8H); MS [M- Br]⁺: 463; mp : 133 °C.

Example 92**1-Allyl-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2] octane; bromide**

The title compound was synthesised according to method c. The yield of the final step was 360 mg , 66%; ^1H - NMR (DMSO-d₆) : δ 1,40-2,30 (m, 5H), 3,00-3,41 (m, 5H), 3,81-3,92 (m, 3H), 5,04 (m, 3H), 5,61 (m, 2H), 5,93-6,05 (m, 1H), 6,93-6,96 (m, 2H), 7,24-7,46 (m, 6H); MS [M- Br]⁺: 383; mp : 110 °C.

Example 93**Phenethylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester**

The title compound was synthesised according to method a. The yield of the final step was 1400 mg , 17%; ^1H - NMR (DMSO-d₆) : δ 1,10-1,60 (m, 4H), 1,83 (s, 1H), 2,40-2,70 (m, 5H), 2,78 (m, 2H), 3,00-3,08 (m, 1H), 3,87 (m, 2H), 4,58 (m, 1H), 7,16-7,40 (m, 10H); MS [M+1]⁺ : 351.

Example 94**1-Methyl-3-(R)(phenethylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide**

The title compound was synthesised according to method c. The yield of the final step was 140 mg , 73%; ^1H - NMR (DMSO-d₆) : δ 1,40-2,30 (m, 5H), 2,80 (m, 2H), 2,94 (s, 3H), 3,10-3,50 (m, 5H), 3,78-3,95 (m, 3H), 4,89 (m, 1H), 7,16-7,41 (m, 10H); MS [M- Br]⁺: 365; mp : 203 °C.

Example 95

1-Allyl-3-(R)(phenethylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
5 was 11 mg , 35%; MS [M- CF₃COO]⁺: 391.

Example 96

3-(R)(Phenethylphenylcarbamoyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2] octane; trifluoroacetate

10 The title compound was synthesised according to method d. The yield of the final step
was 16 mg , 41%; MS [M- CF₃COO]⁺: 485.

Example 97

3-(R)(Phenethylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2] octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
was 15 mg , 40%; ¹H- NMR (DMSO-d₆) : δ 1,45-2,18 (m, 5H), 2,81 (m, 2H), 3,28-3,70
(m, 7H), 3,80-4,02 (m, 3H), 4,43 (m, 2H), 4,95 (m, 1H), 6,98-7,04 (m, 2H), 7,16-7,40 m,
13H); MS [M- CF₃COO]⁺: 471

20

Example 98

3-(R)(Phenethylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2] octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
25 was 14 mg , 37%; ¹H- NMR (DMSO-d₆) : δ 1,45-2,20 (m, 7H), 2,59 (m, 2H), 2,81 (m,
2H), 3,05-3,5 (m, 7H), 3,78-3,89 (m, 3H), 4,91 (m, 1H), 7,17-7,42 (m, 15H); MS [M-
CF₃COO]⁺: 469.

Example 99

30 **3-(R)(Phenethylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2] octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 4 mg , 11%; MS [M- CF₃COO]⁺: 467.

35 **Example 100**

1-(2-Benzylxyethyl)-3-(R)(phenethylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2] octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 14 mg , 36%; MS [M- CF₃COO]⁺: 485.

Example 101

- 5 **1-[3-(3-Hydroxyphenoxy)propyl]-3-(R)(phenethylphenylcarbamoyloxy)-1-azonia
bicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 14 mg , 35%; ¹H- NMR (DMSO-d₆) : δ 1,45-2,20 (m, 7H), 2,82 (m, 2H), 3,05-3,50 (m, 7H), 3,83-3,99 (m, 5H), 4,94 (m, 1H), 6,33-6,39 (m, 3H), 7,04-7,09 (m, 1H), 7,18-10 7,44(m, 10H), 9,49 (s, OH); MS [M- CF₃COO]⁺: 501.

Example 102

- 15 **1-Heptyl-3-(R)(phenethylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane;
trifluoroacetate**

15 The title compound was synthesised according to method d. The yield of the final step was 15 mg , 42%; ¹H- NMR (DMSO-d₆) : δ 0,88 (m, 3H), 1,28 (m, 8H), 1,55-2,20 (m, 7H), 2,82 (m, 2H), 3,00-3,50 (m, 7H), 3,68-3,89 (m, 3H), 4,92 (m, 1H), 7,18-7,43 (m, 10H); MS [M- CF₃COO]⁺: 449.

20 **Example 103**

- 3-(R)(Phenethylphenylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo
[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 15 mg , 39%; MS [M- CF₃COO]⁺: 475.

25

Example 104

- Pentylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester**

The title compound was synthesised according to method a. The yield of the final step was 620 mg , 9%; ¹H- NMR (DMSO-d₆) : δ 0,83 (m, 3H), 1,22-1,30 (m, 5H), 1,43-1,56 (m, 5H), 1,83 (s, 1H), 2,42-2,65 (m, 5H), 3,01-3,06 (m, 1H), 3,59-3,65 (m, 2H), 4,49 (m, 1H), 7,22-7,41 (m, 5 H); MS [M+1]⁺: 317.

Example 105

35 **1-Methyl-3-(R)(pentylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane;
bromide**

The title compound was synthesised according to method c. The yield of the final step was 130 mg , 68%; ¹H- NMR (DMSO-d₆) : δ 0,81 (m, 3H), 1,21 (m, 5H), 1,45-2,20 (m,

6H), 2,93 (s, 3H), 3,10-3,70 (m, 7H), 3,80 (m, 1 H), 4,88 (m, 1H), 7,24-7,41 (m, 5H); MS [M-Br]⁺: 331.

Example 106

- 5 **1-Allyl-3-(R)(pentylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 10 mg , 35%; ¹H- NMR (DMSO-d₆): δ 0,83 (m, 3H), 1,21-1,28 (m, 4H), 1,46 (m, 3H), 1,54-1,91 (m, 3H), 2,30 (m, 1H), 3,28-3,41 (m, 5H), 3,78-3,92 (m, 5H), 4,94 (m, 1H), 5,54-5,64 (m, 2H), 5,98 (m, 1H), 7,26-7,43 (m, 5H); MS [M- CF₃COO]⁺: 357.

Example 107

- 3-(R)(Pentylphenylcarbamoyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2] octane; trifluoroacetate

15 The title compound was synthesised according to method d. The yield of the final step was 13 mg , 36%; MS [M- CF₃COO]⁺: 451.

Example 108

- 3-(R)(Pentylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2] octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 14 mg , 40%; ¹H- NMR (DMSO-d₆): δ 0,82 (m, 3H), 1,23 (m, 4H), 1,46 (m, 3H), 1,54-1,91 (m, 3H), 2,25 (s, 1H), 3,28-3,70 (m, 9H), 3,98 (m, 1H), 4,43 (m, 2H), 4,95 (m, 1H), 6,98-7,04 (m, 3H), 7,23-7,4 (m, 7H); MS [M- CF₃COO]⁺: 437.

25

Example 109

- 3-(R)(Pentylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2] octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 13 mg , 37%; ¹H- NMR (DMSO-d₆): δ 0,82 (m, 3H), 1,20-1,25 (m, 5H), 1,44 (m, 3H), 1,68-2,13 (m, 7H), 2,58 (m, 2H), 3,00-3,41 (m, 5H), 3,54-3,69 (m, 2H), 3,79-3,85 (m, 1H), 4,92 (m, 1H), 7,20-7,42 (m, 10H); MS [M- CF₃COO]⁺: 435.

Example 110

- 35 **3-(R)(Pentylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 4 mg , 12%; MS [M- CF₃COO]⁺: 433.

Example 111

- 5 **1-(2-Benzylxyethyl)-3-(R)(pentylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 15 mg , 42%; MS [M- CF₃COO]⁺: 451.

10 **Example 112**

- 1-[3-(3-Hydroxyphenoxy)propyl]-3-(R)(pentylphenylcarbamoyloxy)-1-azonia bicyclo [2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 12 mg , 32%; MS [M- CF₃COO]⁺: 467.

15

Example 113

- 1-Heptyl-3-(R)(pentylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 15 mg , 45%; MS [M- CF₃COO]⁺: 415.

Example 114

- 3-(R)(Pentylphenylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo [2.2.2]octane; trifluoroacetate**

25 The title compound was synthesised according to method d. The yield of the final step was 13 mg , 37%; ¹H- NMR (DMSO-d₆): δ 0,82 (m, 3H), 1,22-1,26 (m, 5H), 1,46 (m, 3H), 1,60-2,14 (m, 7H), 2,82 (m, 2H), 3,20-3,41 (m, 5H), 3,50-3,70 (m, 2H), 3,82 (m, 1H), 4,92 (m, 1H), 6,93-6,99 (m, 2 H), 7,25-7,43 (m, 6H); MS [M- CF₃COO]⁺: 441.

30 **Example 115**

- Pent-4-enylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester**

The title compound was synthesised according to method a. The yield of the final step was 690 mg , 14%; ¹H- NMR (DMSO-d₆): δ 1,10-1,60 (m, 6 H), 1,84 (bs, 1H), 1,97-2,04 (m, 2H), 2,45-2,65 (m, 5H), 3,02-3,10 (m, 1H), 3,29-3,66 (m, 2H), 4,59 (m, 1H), 4,61-5,00 (m, 2H), 5,70-5,84 (m, 1H), 7,22-7,42 (m, 5H); MS [M+1]⁺: 315.

Example 116

1-Allyl-3-(R)(pent-4-enylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
5 was 10 mg , 35%; MS [M- CF₃COO]⁺: 355.

Example 117

3-(R)(Pent-4-enylphenylcarbamoyloxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

10 The title compound was synthesised according to method d. The yield of the final step was 15 mg , 42%; ¹H- NMR (DMSO-d₆): δ 1,50-2,20 (m, 11H), 3,23-3,47 (m, 7H), 3,56-3,73 (m, 2H), 3,87 (m, 1H), 4,03 (m, 2H), 4,92-4,95 (m, 2H), 5,00 (m, 1H), 5,70-5,82 (m, 1H), 6,93-6,99 (m, 2H), 7,26-7,44 (m, 8H); MS [M- CF₃COO]⁺: 449.

15 **Example 118**

3-(R)(Pent-4-enylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
was 13 mg , 37%; ¹H- NMR (DMSO-d₆): δ 1,55 (m, 2H), 1,65-2,20 (m, 7H), 3,28-3,75
20 (m, 9H), 3,98 (m, 1H), 4,43 (bs, 2H), 4,92-4,99 (m, 3H), 5,70-5,83 (m, 1H), 6,98-7,04
(m, 3H), 7,24-7,40 (m, 7H); MS [M- CF₃COO]⁺: 435.

Example 119

3-(R)(Pent-4-enylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
was 13 mg , 37%; ¹H- NMR (DMSO-d₆): δ 1,56 (m, 3H), 1,70-2,14 (m, 8H), 2,58 (m,
2H), 3,19-3,41 (m, 7H), 3,56-3,71 (m, 2H), 3,81 (m, 1H), 4,92-4,99 (m, 3H), 5,70-5,83
(m, 1H), 7,20-7,43 (m, 10H); MS [M- CF₃COO]⁺: 433.

30

Example 120

3-(R)(Pent-4-enylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
35 was 4 mg , 12%; MS [M- CF₃COO]⁺: 431.

Example 121

1-(2-Benzylxyethyl)-3-(R)(pent-4-enylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
5 was 16 mg , 44%; MS [M- CF₃COO]⁺: 449.

Example 122

**1-[3-(3-Hydroxyphenoxy)propyl]-3-(R)(pent-4-enylphenylcarbamoyloxy)-1-azonia
bicyclo[2.2.2]octane; trifluoroacetate**

10 The title compound was synthesised according to method d. The yield of the final step
was 12 mg , 32%; MS [M- CF₃COO]⁺: 465.

Example 123

**1-Heptyl-3-(R)(pent-4-enylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane;
trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 3 mg , 9%; MS [M- CF₃COO]⁺: 413.

Example 124

20 **1-Methyl-3-(R)(pent-4-enylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane;
trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 13 mg , 49%; MS [M- CF₃COO]⁺: 429.

25 Example 125

3-(R)(Pent-4-enylphenylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
was 15 mg , 43%; ¹H- NMR (DMSO-d₆): δ 1,40-2,20 (m, 11H), 2,82 (m, 2H), 3,05-3,5
30 (m, 7H), 3,58-3,86 (m, 3H), 4,92-4,95 (m, 2H) 5,00 (m, 1H), 5,70-5,84 (m, 1H), 6,93-
7,00 (m, 2H), 7,26-7,44 (m, 6H); MS [M- CF₃COO]⁺: 439.

Example 126

Phenylthiophen-3-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

35 The title compound was synthesised according to method a. The yield of the final step
was 2000 mg , 15%; ¹H- NMR (DMSO-d₆): δ 1,10-1,60 (m, 4H), 1,84 (bs, 1H), 2,46-

2,62 (m, 5H), 3,02-3,10 (m, 1H), 4,62-4,67 (m, 1H), 4,84 (s, 2H), 6,99 (m, 1H), 7,18-7,36 (m, 6H), 7,47-7,50 (m, 1H); MS [M+1]⁺: 343.

Example 127

- 5 **1-Allyl-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 8 mg, 26%; ¹H-NMR (DMSO-d₆): δ 1,45-2,00 (m, 4H), 2,21 (bs, 1H), 3,04-3,42 (m, 5H), 3,78-3,91 (m, 3H), 4,87 (s, 2H), 5,02 (m, 1H), 5,54-5,64 (m, 2H), 5,91-6,02 (m, 1H), 7,00-7,02 (m, 1H), 7,22-7,39 (m, 6H), 7,50-7,52 (m, 1H); MS [M- CF₃COO]⁺: 383.

Example 128

- 15 **1-(3-Phenoxypropyl)-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azonia bicyclo[2.2.2]octane; trifluoroacetate**

15 The title compound was synthesised according to method d. The yield of the final step was 12 mg, 31%; MS [M- CF₃COO]⁺: 477.

Example 129

- 20 **1-(3-Phenylpropyl)-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azonia bicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 15 mg, 41%; ¹H-NMR (DMSO-d₆): δ 1,45-2,18 (m, 7H), 2,59 (m, 2H), 3,02-3,44 (m, 7H), 3,84 (m, 1H), 4,87 (s, 2H), 4,99 (m, 1H), 7,00 (m, 1H), 7,21-7,38 (m, 11H), 7,47-7,50 (m, 1H); MS [M- CF₃COO]⁺: 461.

25

Example 130

- 18 **1-(3-Phenylallyl)-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

30 The title compound was synthesised according to method d. The yield of the final step was 4 mg, 11%; MS [M- CF₃COO]⁺: 459.

Example 131

- 18 **1-(2-Benzylxyethyl)-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azonia bicyclo[2.2.2]octane; trifluoroacetate**

35 The title compound was synthesised according to method d. The yield of the final step was 16 mg, 42%; MS [M- CF₃COO]⁺: 477.

Example 132

1-[3-(3-Hydroxyphenoxy)propyl]-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step
5 was 13 mg , 33%; MS [M- CF₃COO]⁺: 493.

Example 133

1-Heptyl-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

10 The title compound was synthesised according to method d. The yield of the final step was 12 mg , 34%; ¹H- NMR (DMSO-d₆): δ 0,88 (m, 3H), 1,28 (m, 8H), 1,60-2,19 (m, 7H), 3,00-3,41 (m, 7H), 3,83 (m, 1H), 4,88 (s, 2H), 5,99 (m, 1H), 7,01 (m, 1H), 7,21-7,39 (m, 6H), 7,49-7,52 (m, 1H); MS [M- CF₃COO]⁺: 441.

15 **Example 134**

1-Methyl-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 12 mg , 42%; MS [M- CF₃COO]⁺: 357.

20

Example 135

3-(R)(Phenylthiophen-3-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide

The title compound was synthesised according to method c. The yield of the final step
25 was 500 mg , 78%; ¹H- NMR (DMSO-d₆): δ 1,45-2,19 (m, 7H), 2,83 (m, 2H), 3,04-3,13 (m, 1H), 3,19-3,46 (m, 6H), 3,83-3,90 (m, 1H), 4,88 (s, 2H), 4,99 (m, 1H), 6,94 (m, 3H), 7,20-7,40 (m, 7H), 7,49 (m, 1H); MS [M- Br]⁺: 467; mp : 110 °C.

Example 136

30 **3-(R)(Phenylthiophen-3-ylmethylcarbamoyloxy)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane; bromide**

The title compound was synthesised according to method c. The yield of the final step
35 was 350 mg , 63%; ¹H- NMR (DMSO-d₆): δ 1,45-2,20 (m, 5H), 3,27 (m, 1H), 3,40-3,80 (m, 6H), 4,00-4,06 (m, 1H), 4,44 (bs, 2H), 4,87 (s, 2H), 5,02 (m, 1H), 6,99-7,04 (m, 4H), 7,20-7,38 (m, 8H), 7,48 (m, 1H); MS [M- Br]⁺: 463; mp : 131 °C.

Example 137**Butylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester**

The title compound was synthesised according to method a. The yield of the final step
5 was 1300 mg , 29%; ¹H- NMR (DMSO-d₆): δ 0,85 (m, 3H), 1,19-1,68 (m, 8H), 1,92
(m,1H), 2,49-2,64 (m, 5H), 3,05-3,22 (m, 3H); 4,56-4,62 (m, 3H), 6,95-7,04 (m, 2H),
7,42-7,44 (m, 1H); MS [M+1]⁺: 323.

Example 138**10 1-Allyl-3-(R)(butylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]
octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 10 mg , 23%; ¹H- NMR (DMSO-d₆): δ 0,86 (m, 3H), 1,20-1,26 (m, 2H), 1,42-1,49
(m, 2H), 1,58-2,05 (m, 4H), 2,32 (bs, 1H), 3,20-3,41 (m, 7H), 3,74-3,94 (m, 3H), 4,51-
15 4,72 (m, 2H), 4,99 (m, 1H), 5,55-5,64 (m, 2H), 5,87-6,10 (m, 1H), 6,99 (m, 1H), 7,08
(m, 1H), 7,46.(m, 1H); MS [M- CF₃COO]⁺: 363.

Example 139**20 3-(R)(Butylthiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo
[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 13 mg , 25%; ¹H- NMR (DMSO-d₆): δ 0,85 (m, 3H), 1,19-1,26 (m, 2H), 1,41-1,50
(m, 2H), 1,75-2,10 (m, 6H), 2,30 (bs, 1H), 2,59 (m, 2H), 3,10-3,50 (m, 9H), 3,83 (m, 1
H), 4,50-4,74 (m, 2H), 4,97 (m, 1H), 6,97 (m, 1H), 7,07 (m, 1H), 7,20-7,35 (m, 5H), 7,43
25 (m, 1H); MS [M- CF₃COO]⁺: 441.

Example 140**bis-Thiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester**

The title compound was synthesised according to method a. The yield of the final step
30 was 340 mg , 7%; ¹H- NMR (DMSO-d₆): δ 1,28-1,31 (m, 1H), 1,45-1,72 (m, 3H), 1,94-
1,97 (m, 1H), 2,49-2,71 (m, 5H), 3,06-3,14 (m, 1H), 4,50-4,57 (m, 4H), 4,62-4,69 (m,
1H), 6,96-7,06 (m, 4H), 7,44-7,46 (m, 2H); MS [M+1]⁺: 363.

Example 141**35 1-Allyl-3-(R)(bis-thiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane;
trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 9 mg , 19%; ¹H- NMR (DMSO-d₆): δ 1,70-2,06 (m, 4H), 2,35 (bs, 1H), 3,25-3,50 (m, 5H), 3,80-3,94 (m, 3H), 4,54-4,71 (m, 4H), 5,10 (m, 1H), 5,55-5,65 (m, 2H), 5,87-6,10 (m, 1H), 6,98-7,01 (m, 2H), 7,06-7,10 (m, 2H), 7,47-7,48 (m, 2H); MS [M-CF₃COO]⁺: 403.

Example 142

3-(R)(bis-thiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; bromide

10 The title compound was synthesised according to method c. The yield of the final step was 690 mg , 82%; ¹H- NMR (DMSO-d₆): δ 1,78-2,10 (m, 6H), 2,34 (bs, 1H), 2,53-2,63 (m, 2H), 3,23-3,48 (m, 7H), 3,88 (m, 1H), 4,53-4,74 (m, 4H), 5,05 (m, 1H), 6,98-7,01 (m, 2H), 7,02-7,11 (m, 2H), 7,21-7,37 (m, 5H), 7,44-7,48 (m, 2H); MS [M-Br]⁺: 481.

15 **Example 143**

Furan-2-ylmethyl-2-thiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesised according to method a. The yield of the final step was 700 mg , 10%; ¹H- NMR (DMSO-d₆): δ 1,10-1,34 (m, 1H), 1,44-1,67 (m, 3H), 1,93 (bs, 1H), 2,50-2,70 (m, 5H), 3,05-3,12 (m, 1H), 3,37-4,40 (m, 2H), 4,57-4,66 (m, 3H), 6,26-6,42 (m, 2H), 6,95-7,03 (m, 2H), 7,45 (m, 1H), 7,61 (m, 1H); MS [M+1]⁺: 347.

Example 144

1-Allyl-3-(R)(furan-2-ylmethylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

25 The title compound was synthesised according to method d. The yield of the final step was 7 mg , 15%; MS [M- CF₃COO]⁺: 387.

Example 145

3-(R)(Furan-2-ylmethylthiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 11 mg , 20%; ¹H- NMR (DMSO-d₆): δ 1,70-2,10 (m, 6H), 2,31 (bs, 1H), 2,59 (m, 2H), 3,15-3,50 (m, 7H), 3,84 (m, 1H), 4,36-4,56 (m, 4H), 5,03 (m, 1H), 6,32-6,44 (m, 2H), 6,92-7,08 (m, 2H), 7,20-7,35 (m, 5H), 7,41-7,46 (m, 1H), 7,59-7,62 m, 1H); MS [M- CF₃COO]⁺: 465.

Example 146**3-(R)(bis-thiophen-2-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-azonia
bicyclo[2.2.2]octane; bromide**

- 5 The title compound was synthesised according to method c. The yield of the final step was 690 mg , 81%; ^1H - NMR (DMSO-d₆): δ 1,78-2,10 (m, 6H), 2,34 (bs, 1H), 2,82 (m, 2H), 3,21-3,46 (m, 7H), 3,89 (m, 1H), 4,54 (m, 4H), 5,06 (m, 1H), 6,95-7,01 (m, 4H), 7,07-7,11 (m, 2H), 7,38-7,49 (m, 3H); MS [M-Br]⁺: 487; mp : 143 °C.

10 Example 147**Allylthiophen-2-ylmethylecarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester**

- The title compound was synthesised according to method a. The yield of the final step was 3220 mg , 30%; ^1H - NMR (DMSO-d₆): δ 1,20-1,33 (m, 1H), 1,45-1,80 (m, 3H), 1,93 (bs, 1H), 2,49-2,72 (m, 5H), 3,05-3,09 (m, 1H), 3,81-3,83 (m, 2H), 3,83-4,55 (m, 3H), 15 5,14 (m, 2H), 5,70-5,82 (m, 1H), 6,96-7,04 (m, 2H), 7,44-7,45 (m, 1H); MS [M+1]⁺: 307.

Example 148**1-Allyl-3-(R)(allylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]****20 octane; trifluoroacetate**

- The title compound was synthesised according to method d. The yield of the final step was 10 mg , 24%; ^1H - NMR (DMSO-d₆): δ 1,80-2,10 (m, 4H), 2,32 (bs, 1H), 3,20-3,50 (m, 5H), 3,75-3,94 (m, 5H), 4,5-4,69 (m, 2H), 5,01 (m, 1H), 5,10-5,23 (m, 2H), 5,51-5,65 (m, 2H), 5,70-5,85 (m, 1H), 5,90-6,08 (m, 1H), 6,95-7,10 (m, 2H), 7,47 (m, 1H); 25 MS [M- CF₃COO]⁺: 347.

Example 149**3-(R)(Allylthiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo
[2.2.2]octane; trifluoroacetate**

- 30 The title compound was synthesised according to method d. The yield of the final step was 11 mg , 22%; ^1H - NMR (DMSO-d₆): δ 1,74-2,10 m, 6H), 2,31 (bs, 1H), 2,59 (m, 2H), 3,16-3,56 (m, 7H), 3,76-3,90 (m, 3H), 4,48-4,71 (m, 2H), 4,99 (m, 1H), 5,11-5,23 (m, 2H), 5,72-5,83 (m, 1H), 6,98 (m, 1H), 7,06-7,07(m, 1H), 7,20-7,35 (m, 5H), 7,44 (m, 1H); MS [M- CF₃COO]⁺: 425.

Example 150

Cyclopentylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesised according to method a. The yield of the final step
5 was 2250 mg , 33%; ¹H- NMR (DMSO-d₆): δ 1,20-1,40 (m, 1H), 1,45-1,72 (m, 11H),
1,89 (bs, 1H), 2,45-2,62 (m, 5H), 3,03-3,10 (m, 1H), 4,22 (bs, 1H), 4,50-4,56 (m, 3H),
6,93-6,99 (m, 2H), 7,38 (m, 1H); MS [M+1]⁺: 335.

Example 151

10 **1-Allyl-3-(R)(cyclopentylthiophen-2-ylmethylcarbamoyloxy)-1-azoniabicyclo
[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 10 mg , 22%; ¹H- NMR (DMSO-d₆): δ 1,40-2,05 (m, 12H), 2,27 (bs, 1H), 3,03,3,42
(m, 5H), 3,70-3,95 (m, 3H), 4,15-4,35 (m, 1H), 5,58 (m, 2H), 4,99 (m, 1H), 5,54-5,65 (m,
15 2H), 5,87-6,10 (m, 1H), 6,97 (m, 1H), 7,03 (m, 1H), 7,41-7,43 (m, 1H); MS [M-
CF₃COO]⁺: 375.

Example 152

20 **3-(R)(Cyclopentylthiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azonia
bicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step
was 13 mg , 24%; ¹H- NMR (DMSO-d₆): δ 1,40-2,10 (m, 14H), 2,25 (bs, 1H), 2,58 (m,
2H), 2,95-3,50 (m, 7H), 3,81 (m, 1H), 4,26 (m, 1H), 4,50-4,70 (m, 2H), 4,97 (m, 1H),
6,93 (m, 1H), 7,03 (m, 1H), 7,20-7,40 (m, 6H); MS [M- CF₃COO]⁺: 453.

25

Example 153

Furan-2-ylmethylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

The title compound was synthesised according to method a. The yield of the final step
was 1400 mg , 18%; ¹H- NMR (DMSO-d₆): δ 1,19-1,60 (m, 4H), 1,84 (bs, 1H), 2,44-
30 2,57 (m, 5H), 3,01-3,09 (m, 1H), 4,63 (m, 1H), 4,82 (s, 2H), 6,21 (m, 1H), 6,36 (m, 1H),
7,20-7,37 (m, 5H), 7,59 (m, 1H); MS [M+1]⁺: 327.

Example 154

1-Allyl-3-(R)(furan-2-ylmethylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane;

35 **trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 7 mg , 16%; ^1H - NMR (DMSO-d₆): δ ; MS [M- CF₃COO]⁺: 367.

Example 155

- 5 **3-(R)(Furan-2-ylmethylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 11 mg , 21%; ^1H - NMR (DMSO-d₆): δ 1,65-2,10 (m, 6H), 2,19 (bs, 1H), 2,59 (m, 2H), 3,10-3,50 (m, 7H), 3,83 (m, 1H), 4,85 (bs, 2H), 4,98 (m, 1H), 6,26 (m, 1H), 6,36 (m, 1H), 7,20-7,39 (m, 10H), 7,59 (m, 1H); MS [M- CF₃COO]⁺: 445.

Example 156

bis-Furan-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester

15 The title compound was synthesised according to method a. The yield of the final step was 2100 mg , 22%; ^1H - NMR (DMSO-d₆): δ 1,20-1,70 (m, 4H), 1,89 (bs, 1H), 2,45-2,71 (m, 5H), 3,00-3,12 (m, 1H), 4,40 (m, 4H), 4,62 (m, 1H), 6,22-6,40 (m, 4H), 7,59 (m, 2H); MS [M+1]⁺: 331.

Example 157

- 20 **1-Allyl-3-(R)(bis-furan-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate**

The title compound was synthesised according to method d. The yield of the final step was 7 mg , 16%; ^1H - NMR (DMSO-d₆): δ ; MS [M- CF₃COO]⁺: 371.

25 **Example 158**

3-(R)(bis-furan-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

The title compound was synthesised according to method d. The yield of the final step was 11 mg , 20%; ^1H - NMR (DMSO-d₆): δ 1,70-2,10 (m, 6H), 2,29 (bs, 1H), 2,59 (m, 2H), 3,10-3,50 (m, 7H), 3,82 (m, 1H), 4,32-4,54 (m, 4H), 5,01 (m, 1H), 6,29-6,41 (m, 4H), 7,20-7,35 (m, 5H), 7,57-7,61 (m, 2H); MS [M- CF₃COO]⁺: 449.

Example 159

Benzylphenylcarbamic acid 1-azabicyclo[2.2.1]hept-4-yl ester

35 The title compound was synthesised according to method a. The yield of the final step was 4.86 mg , 1.3%, as formiate; ^1H - NMR (DMSO-d₆): δ 1,86 (m, 4H), 2,65 (s, 2H),

2,77 (bs, 2H), 3,03 (bs, 2H), 4,84 (s, 2H), 7,14-7,32 (m, 10H), 8,19 (s, 1H); MS [M-HCOO]⁺: 323;

Example 160

5 **Benzylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-4-yl ester**

The title compound was synthesised according to method a. The yield of the final step was 2.56 mg , 1%, as formiate; ¹H- NMR (DMSO-d₆): δ 1,81 (m, 6H), 2,83 (m, 6H), 4,81 (s, 2H), 7,14-7,32 (m, 10H), 8,24. (s, 1H); MS [M-HCOO]⁺: 337

10 The examples 161 to 165 illustrate pharmaceutical compositions according to the present invention and procedures for their preparation.

Example 161

Preparation of a pharmaceutical composition: tablets

15 **Formulation:**

Compound of the present invention	5.0 mg
Lactose.....	113.6 mg
Microcrystalline cellulose.....	28.4 mg
Light silicic anhydride.....	1.5 mg.
20 Magnesium stearate.....	1.5 mg

Using a mixer machine, 15 g of the compound of the present invention was mixed with 340.8 g of lactose and 85.2 g of microcrystalline cellulose. The mixture was subjected to compression moulding using a roller compactor to give a flake-like compressed material. The flake-like compressed material was pulverized using a hammer mill, and the pulverized material was screened through a 20 mesh screen. A 4.5 g portion of light silicic anhydride and 4.5 g of magnesium stearate were added to the screened material and mixed. The mixer product was subjected to a tablets making machine equipped with a die/punch system of 7.5 mm in diameter, thereby obtaining 3,000 tablets each having 150 mg in weight.

Example 162

Preparation of a pharmaceutical composition: tablets coated

Formulation:

35 Compound of the present invention.....	5.0 mg
Lactose.....	95.2 mg
Corn starch.....	40.8 mg

	Polyvinylpyrrolidone	7.5 mg
	Magnesium stearate.....	1.5 mg
	Hydroxypropylcellulose.....	2.3 mg
	Polyethylene glycol	0.4 mg
5	Titanium dioxide.....	1.1 mg
	Purified talc.....	0.7 mg

Using a fluidized bed granulating machine, 15 g of the compound of the present invention was mixed with 285.6 g of lactose and 122.4 g of corn starch. Separately, 10 22.5 g of polyvinylpyrrolidone was dissolved in 127.5 g of water to prepare a binding solution. Using a fluidized bed granulating machine, the binding solution was sprayed on the above mixture to give granulates. A 4.5 g portion of magnesium stearate was added to the obtained granulates and mixed. The obtained mixture was subjected to a tablet making machine equipped with a die/punch biconcave system of 6.5 mm in 15 diameter, thereby obtaining 3,000 tablets, each having 150 mg in weight. Separately, a coating solution was prepared by suspending 6.9 g of hydroxypropylmethylcellulose 2910, 1.2 g of polyethylene glycol 6000, 3.3 g of titanium dioxide and 2.1 g of purified talc in 72.6 g of water. Using a High Coated, the 3,000 20 tablets prepared above were coated with the coating solution to give film-coated tablets, each having 154.5 mg in weight.

Example 163

Preparation of a pharmaceutical composition: liquid inhalant

Formulation:

25	Compound of the present invention.....	400 µg
	Physiological saline.....	1 ml

A 40 mg portion of the compound of the present invention was dissolved in 90 ml of physiological saline, and the solution was adjusted to a total volume of 100 ml with the 30 same saline solution, dispensed in 1 ml portions into 1 ml capacity ampoule and then sterilized at 115° for 30 minutes to give liquid inhalant.

Example 164

Preparation of a pharmaceutical composition: powder inhalant

35 Formulation:

	Compound of the present invention.....	200 µg
	Lactose.....	4,000 µg

A 20 g portion of the compound of the present invention was uniformly mixed with 400 g of lactose, and a 200 mg portion of the mixture was packed in a powder inhaler for exclusive use to produce a powder inhalant.

5

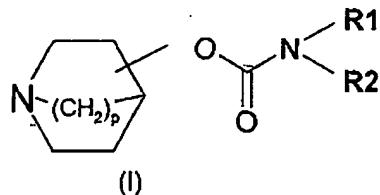
Example 165**Preparation of a pharmaceutical composition: inhalation aerosol.****Formulation:**

Compound of the present invention.....	200 µg
10 Dehydrated (Absolute) ethyl alcohol USP.....	8,400 µg
1,1,1,2-Tetrafluoroethane (HFC-134A).....	46,810 µg

The active ingredient concentrate is prepared by dissolving 0.0480 g of the compound of the present invention in 2.0160 g of ethyl alcohol. The concentrate is added to an 15 appropriate filling apparatus. The active ingredient concentrate is dispensed into aerosol container, the headspace of the container is purged with Nitrogen or HFC-134A vapor (purging ingredients should not contain more than 1 ppm oxygen) and is sealed with valve. 11.2344 g of HFC-134A propellant is then pressure filled into the sealed container.

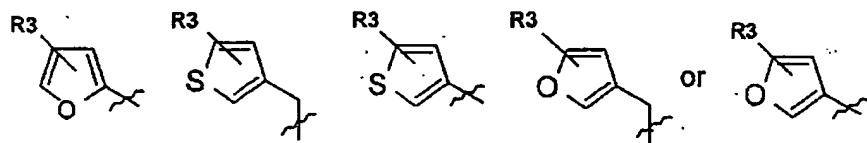
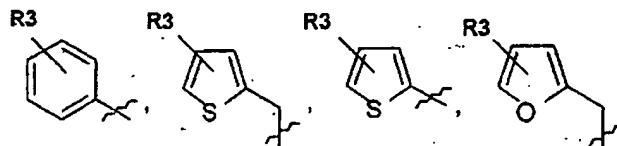
CLAIMS

1. A compound which is a carbamate of formula (I):



5 wherein

R1 represents

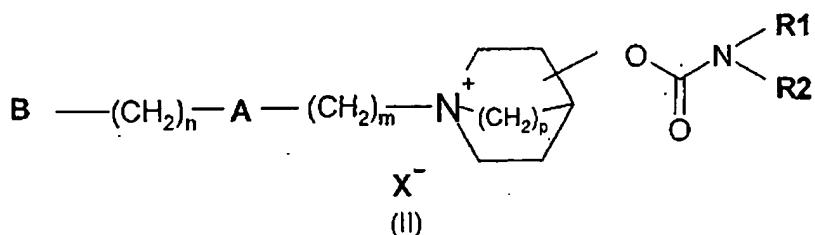


10

R3 represents a hydrogen or halogen atom, or a straight or branched lower alkyl group or a cyano group;

15 R2 represents a benzyl, phenethyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl or thiophen-3-ylmethyl group or a straight or branched alkyl group having 3 to 8 carbon atoms, an alkenyl group having 3 to 8 carbon atoms, or a cycloalkyl group of 3 to 6 carbon atoms;
 p is 1 or 2 and the substitution in the azoniabicyclic ring may be in the 2, 3 or 4 position including all possible configurations of the asymmetric carbons;
 20 or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 which is represented by formula (II):



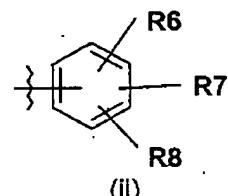
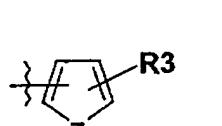
wherein R1, R2 and p are as defined in claim 1;

m is an integer from 0 to 8;

5 A represents a -CH₂-, -CH=CR4-, -CR4=CH-, -CO-, -O-, -S-, -S(O)-, -SO₂-, -NR4-, or -CR4R5- group, wherein R4 and R5 each independently represent a hydrogen atom, a straight or branched lower alkyl group, or R4 and R5 together form an alicyclic ring;

n is an integer from 0 to 4;

10 B represents a hydrogen atom, an alkoxy group, a cycloalkyl group, -COOR4 or -OOCR4 wherein R4 is as defined above, or a cyano group, a naphthalenyl group, a 5,6,7,8-tetrahydronaphthalenyl group, a biphenyl group, or a group of formula (i) or (ii)



15

wherein Z represents O, N or S;

R3 is as defined above; and

20 R6, R7 and R8 each independently represent a hydrogen or halogen atom, or a hydroxy, phenyl, -OR4, -SR4, -NR4R5, -NHCOR4, -CONR4R5, -CN, -NO₂, -COOR4 or -CF₃ group or a straight or branched, substituted or unsubstituted lower alkyl group;

wherein R4 and R5 each independently represent a hydrogen atom, a straight or branched lower alkyl group, or R4 and R5 together form an alicyclic ring; or R6 and R7 together form an aromatic, alicyclic or heterocyclic ring; and

25 X' represents a pharmaceutically acceptable anion of a mono or polyvalent acid.

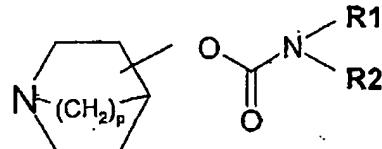
3. A compound according to claim 1 or claim 2, wherein p is 2.

4. A compound according to any one of claims 1 to 3, wherein R1 represents a phenyl, 4-fluorophenyl, 4-methylphenyl, thiophen-2-ylmethyl, thienyl or furan-2-ylmethyl group.
5. A compound according to any one of the preceding claims wherein R2 represents a benzyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, furan-2-ylmethyl, phenethyl, pent-4-enyl, pentyl, butyl, allyl or cyclopentyl group.
6. A compound according to an one of the preceding claims, wherein B represents a hydrogen atom or a substituted or unsubstituted phenyl, pyrrolyl, thienyl or furyl group, or a biphenyl, naphthalenyl, 5,6,7,8-tetrahydronaphthalenyl or benzo[1,3]dioxolyl group.
7. A compound according to claim 6, wherein B represents a substituted or unsubstituted phenyl group and R6, R7 and R8 each independently represent a hydrogen or halogen atom, or a hydroxyl, methyl, -CH₂OH, -OMe, -NMe₂, -NHCOMe, -CONH₂, -CN, -NO₂, -COOMe, or -CF₃ group.
8. A compound according to claim 7, wherein B represents a phenyl, 4-fluorophenyl or 3-hydroxyphenyl group.
9. A compound according to any one of the preceding claims, wherein n= 0 or 1; m is an integer from 1 to 6; and A represents a -CH₂-, -CH=CH-, -CO-, -NMe-, -O- or -S- group.
10. A compound according to claim 9, wherein m is 1, 2 or 3 and A represents a -CH₂-, -CH=CH-, or -O- group.
11. A compound according to any one of the preceding claims, wherein B-(CH₂)_n-A-(CH₂)_m- represents a group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 3-thiophen-2-ylpropyl, 1-allyl and 1-heptyl.
12. A compound according to any one of the preceding claims, wherein X represents a chloride, bromide, or trifluoroacetate anion.

13. A compound according to any one of the preceding claims, wherein the azoniabicyclo group is substituted in the 3-position.
 14. A compound according to claim 13, wherein the substituent at the 3-position
5 has the (R) configuration.
 15. A compound according to any one of the preceding claims, which is a single isomer.
 - 10 16. A compound according to claim 1 which is:
Benzylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Benzyl(4-fluorophenyl)carbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Benzyl-p-tolylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Butylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
 - 15 Phenylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester.
Phenethylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Pentylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Pent-4-enylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Phenylthiophen-3-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
 - 20 Butylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Bis-thiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Furan-2-ylmethyl-2-thiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Allylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
 - 25 Cyclopentylthiophen-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Furan-2-ylmethylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Bis-furan-2-ylmethylcarbamic acid 1-azabicyclo[2.2.2]oct-3-(R)yl ester
Benzylphenylcarbamic acid 1-azabicyclo[2.2.1]hept-4-yl ester
 - 30 Benzylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-4-yl ester
or a pharmaceutically acceptably salt thereof.
17. A compound according to claim 2 which is:
3-(R)(Benzylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-
35 azoniabicyclo[2.2.2]octane; bromide
1-Allyl-3-(R)(benzylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide

- 3-(R)(Benzylphenylcarbamoyloxy)-1-phenethyl-1-azoniabicyclo[2.2.2]octane;
bromide
- 3-(R)(Benzylphenylcarbamoyloxy)-1-(3-thiophen-2-yl-propyl)-1-
azoniabicyclo[2.2.2] octane; bromide
- 5 3-(R)(Benzylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-
azoniabicyclo[2.2.2]octane; bromide
- 3-(R)(Benzylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-
azoniabicyclo[2.2.2]octane; bromide
- 3-(R)(Butylphenylcarbamoyloxy)-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane;
10 bromide
- 1-Allyl-3-(R)(butylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane; bromide
- 3-(R)(Butylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-
azoniabicyclo[2.2.2]octane; bromide
- 3-(R)(Butylphenylcarbamoyloxy)-1-[3-(3-hydroxyphenoxy)propyl]-1-
15 azoniabicyclo [2.2.2]octane; bromide
- 3-(R)(Butylphenylcarbamoyloxy)-1-[3-(4-fluorophenoxy)propyl]-1-
azoniabicyclo[2.2.2] octane; bromide
- 3-(R)(Butylphenylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-
azoniabicyclo[2.2.2] octane; bromide
- 20 3-(R)(Butylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-
azoniabicyclo[2.2.2]octane; bromide
- 3-(R)(Phenylthiophen-2-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-
azonia bicyclo[2.2.2]octane; bromide
- 1-(2-Phenoxy-ethyl)-3-(R)-(phenyl-thiophen-2-ylmethyl-carbamoyloxy)-1-
25 azoniabicyclo [2.2.2]octane; bromide
- 1-Allyl-3-(R)(phenylthiophen-2-ylmethylcarbamoyloxy)-1-
azoniabicyclo[2.2.2]octane; bromide
- 3-(R)(Phenethylphenylcarbamoyloxy)-1-(2-phenoxyethyl)-1-
azoniabicyclo[2.2.2]octane; trifluoroacetate
- 30 1-Heptyl-3-(R)(pent-4-enylphenylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane;
trifluoroacetate
- 1-Allyl-3-(R)-(phenyl-thiophen-3-ylmethyl-carbamoyloxy)-1-azonia-
bicyclo[2.2.2]octane; trifluoroacetate
- 3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-
35 azonia bicyclo[2.2.2]octane; bromide
- 1-(2-Phenoxyethyl)-3-(R)(phenylthiophen-3-ylmethylcarbamoyloxy)-1-
azoniabicyclo [2.2.2]octane; bromide

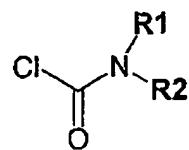
- 3-(R)(Bis-thiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo
[2.2.2]octane; bromide
- 3-(R)(Bis-thiophen-2-ylmethylcarbamoyloxy)-1-(3-thiophen-2-ylpropyl)-1-
azoniabicyclo [2.2.2]octane; bromide
- 5 1-Allyl-3-(R)(allylthiophen-2-ylmethylcarbamoyloxy)-1-
azoniabicyclo[2.2.2]octane; trifluoroacetate
- 3-(R)(Cyclopentylthiophen-2-ylmethylcarbamoyloxy)-1-(3-phenylpropyl)-1-
azonia bicyclo[2.2.2]octane; trifluoroacetate
- 10 3-(R)(Furan-2-ylmethylphenylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo
[2.2.2]octane; trifluoroacetate or
- 1-ALLYL-3-(R)(bis-furan-2-ylmethylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane;
trifluoroacetate.
18. A compound according to any one of the preceding claims characterised in that
it has an IC₅₀ value (nM) for muscarinic M3 receptors of less than 35.
- 15
19. A process for the preparation of a carbamate of formula (I)



20

(I)

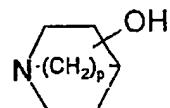
wherein R1, R2 and p are as defined in any one of claims 1, 3 to 5 or 13 to 16,
which process comprises reacting a compound of formula (III):



25

(III)

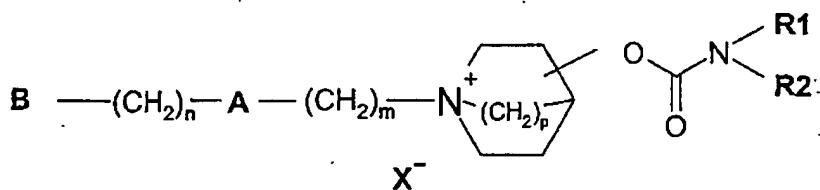
with a compound of formula (IV):



(IV)

5 wherein R1, R2 and p in formulae (III) and (IV) are as defined in any one of claims 1, 3 to 5 or 13 to 16.

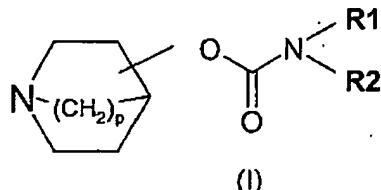
20. A process for producing a salt of formula (II):



10

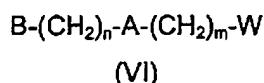
wherein R1, R2, p, m, A, B and X are as defined in any one of claims 1 to 17, which process comprises quaternising the nitrogen atom of the azoniabicyclic ring of a compound of formula (I):

15



20

wherein R1, R2 and p are as defined in any one of claims 1, 3 to 5 or 13 to 16, with an alkylating agent of formula (VI):



25

wherein m, n, A and B are as defined above, and W represents a leaving group.

21. A process according to claim 20, wherein W represents a group X as defined in claim 1 or 12.

22. A process according to claim 20 or claim 21, wherein the resulting reaction mixture is purified by solid phase extraction.
- 5 23. A pharmaceutical composition comprising a compound according to any one of claims 1 to 18 in admixture with a pharmaceutically acceptable carrier or diluent.
- 10 24. A compound according to any one of claims 1 to 18, or a pharmaceutical composition according to claim 23, for use in a method of treatment of the human or animal body by therapy.
- 15 25. Use of a compound according to any one of claims 1 to 18, or a pharmaceutical composition according to claim 23, in the manufacture of a medicament for the treatment of a respiratory, urological or gastrointestinal disease or disorder.
- 20 26. A method of treating of respiratory, urinary or gastrointestinal diseases, which method comprises administering to a human or animal patient in need of treatment an effective amount of a compound according to any one of claims 1 to 18 or a pharmaceutical composition according to claim 23.
- 25 27. A combination product comprising
 - (i) a compound according to any one of claims 1 to 18; and
 - (ii) another compound effective in the treatment of a respiratory, urological or gastrointestinal disease or disorderfor simultaneous, separate or sequential use.
- 30 28. A combination product according to claim 27 comprising
 - (i) a compound according to any one of claims 1 to 18; and
 - (iv) a β_2 agonist, steroid, antiallergic drug, phosphodiesterase IV inhibitor and/or leukotriene D4 (LTD4) antagonistfor simultaneous, separate or sequential use in the treatment of a respiratory disease.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/EP 01/15169

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D453/02 A61K31/439 A61P43/00 C07D471/08
 //((C07D471/08, 221:00, 209:00))

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 747 355 A (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 11 December 1996 (1996-12-11) cited in the application claims	1,23-25
A	EP 0 801 067 A (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 15 October 1997 (1997-10-15) cited in the application claims	1,23-25
P,A	WO 01 04118 A (ALMIRALL PRODESFARMA S.A.) 18 January 2001 (2001-01-18) cited in the application claims	2,23-25

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

23 April 2002

Date of mailing of the international search report

07/05/2002

Name and mailing address of the IBA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl
 Fax: (+31-70) 340-3018

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

In International Application No
PCT/EP 01/15169

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

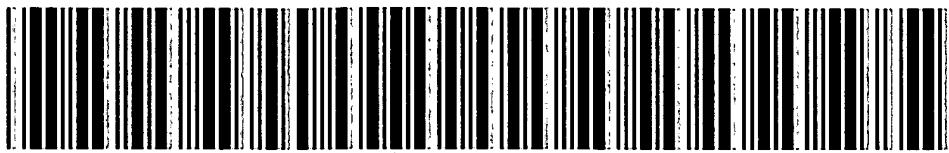
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 02 00652 A (LABORATORIOS S.A.L.V.A.T., S.A.) 3 January 2002 (2002-01-03) * complete document, in particular example 1-7, 10, 13 and 65 * -----	1-25

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/15169

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 747355	A	11-12-1996		AU 685225 B2 AU 1590995 A EP 0747355 A1 CA 2182568 A1 CN 1140447 A HU 76289 A2 WO 9521820 A1		15-01-1998 29-08-1995 11-12-1996 17-08-1995 15-01-1997 28-07-1997 17-08-1995
EP 801067	A	15-10-1997		AU 695616 B2 AU 4355396 A EP 0801067 A1 FI 972775 A JP 3014457 B2 NO 973027 A NZ 298144 A PL 321019 A1 RU 2143432 C1 US 6017927 A CA 2208839 A1 CN 1171109 A ,B HU 77006 A2 WO 9620194 A1 US 6174896 B1		20-08-1998 19-07-1996 15-10-1997 22-08-1997 28-02-2000 28-08-1997 27-04-1998 24-11-1997 27-12-1999 25-01-2000 04-07-1996 21-01-1998 02-03-1998 04-07-1996 16-01-2001
WO 0104118	A	18-01-2001		ES 2165768 A1 AU 6433000 A BR 0012434 A WO 0104118 A2 NO 20020180 A		16-03-2002 30-01-2001 02-04-2002 18-01-2001 13-03-2002
WO 0200652	A	03-01-2002	WO	0200652 A1		03-01-2002

IDS REFERENCES



FOR